Kliiniline küsimus nr 17.

Kas enneaegsete vastsündinute esmasel stabiliseerimisel tuleb parema ravitulemi saavutamiseks hemodünaamika hindamiseks kasutada kindlaid kriteeriume võrreldes kriteeriumite mittekasutamisega?

Kriitilised tulemusnäitajad: lapse peamised tulemusnäitajad

Süstemaatilised ülevaated

Kokkuvõte süstemaatilistest ülevaadetest

Tõendusmaterjali kokkuvõte põhineb 4 süstemaatilisel kirjanudse ülevaate (Dempsey 2007, Ibrahim 2008, Dempsey 2009, Gale 2010), 2 prospektiivsel vaatlus-kohortuuringul (Miletin 2009, Batton 2013), 1 retrospektiivsel kohortuuringul (Dempsey 2009). Vastavad soovitused olid antud ka kahes AGREE-ga kvaliteetseks hinnatud ravijuhendis, aastatest 2011 (Hüpotensiooni ravijuhis USA) ja 2013 (Euroopa RDS ravijuhis).

Käesolevad standardsed lähenemised transitoorsete tsirkulatoorsete probleemide hindamiseks ja raviks enneaegsetel vastsündinutel ei ole tõenduspõhised (Dempsey 2014)[8]. Hüpotensioon on statistiliselt seotud ebasoodsate lühi- ja kaugtoimetega, kirjanduse süstemaatilises ülevaates ei leitud ühtseid, selgeid kriteeriume hüpotensiooni defineerimiseks (Dempsey 2007, Ibrahim 2008)[4,5]. Käesoleva kirjanduse andmetel ei ole võimalik defineerida vererõhu lävväärtust, mis oleks ennustav halvaks kaugtulemuseks või millised terapeutilised vahelesekkumised hüpotensiivsetel enneaegsetel lastel parandaksid ravitulemust ja oleksid kasutoovad või millised peaksid olema normaalsed aktsepteeritavad vererõhunäitajad (Dempsey 2007,2009,2014; Batton 2013, Ibrahim 2008; Hüpotensiooni ravijuhis 2011, Euroopa RDS ravijuhis)[6,4,10,3,7].

Kõrge kvaliteediga randomiseeritud kontrolluuringud vererõhu ravimiseks enneaegsetel vastsündinutel puuduvad.

Hüpotensiooni definitsioon ja täpne ravi varieerub praktikas vastsündinute intensiivravi osakondades (Dempsey 2007,2009,2014; Batton 2013)[4,2,8,1]. “Normaalseks vererõhuks” peaks defineerima rõhku, mis tagab adekvaatse organite perfusiooni (Ibrahim 2008)[5]. Paljud normatiivsed vererõhu referentsväärtused baseeruvad kriteeriumitel nagu sünnikaal, gestatsioonivanus ja postnataalne vanus (Dempsey 2009,2014, Ibrahim 2008)[2,8,5]. Need statistiliselt kindlaks määratud vererõhu väärtused varieeruvad märkimisväärselt, kuna baseeruvad retrospektiivsetel uuringutel, mis on tehtud väikestel kohortidel, väheste andmetega, keskmiselt laias ajavahemikus, mittepiisava vererõhu mõõtmiste arvuga, kombineeritud on invasiivsed ja mitteinvasiivsed mõõtmised. Uuringud on tehtud vastsündinutel, kes sündisid enne perinataalabi parandavate ravivõtete kasutamist (antenataalsed glükokortikoidid), mis vähendavad intraventrikulaarsete hemorraagiate esinemissagedust enneaegsetel (Dempsey 2009, 2014)[2,8].

The Joint Working Group of the British Association of Perinatal Medicine on soovitanud, et **keskmine arteriaalne vererõhk (mm Hg) peaks olema ülevalpool gestatsioonivanust nädalates** (nt. 25. rasedusnädalal sündinud vastsündinul peaks keskmine vererõhk olema > 25 mmHg) [Development of audit measures and guidelines for good practice in the management of the neonatal respiratory distress syndrome 1992]. Vaatamata vähesele tõenduspõhisusele on see kõige sagedasem ja tihti ainuke ravi alustamise kriteerium [Pellicer A et al 2005] (1,2,4,5,8), seda on kasutatud mitmetes randomiseeritud terapeutiliste vahelesekkumise uuringutes, kus see oli ainukeseks liitumiskriteeriumiks (Dempsey 2007, 2009, 2014[4,2,8], Hüpotensiooni ravijuhis 2011, Euroopa RDS ravijuhis 2013).

Vererõhk ei pruugi korreleeruda perfusiooniga. Retrospektiivses kohortuuringus hinnati kombineeritud parameetrite efektiivsust (kliinilised tunnused, metaboolne atsidoos, absoluutse vererõhu väärtused) hüpotensiooni ravi alustamisel väga väikestel enneaegsetel, vererõhk stabiliseerus neil spontaanselt esimese 24 tunni jooksul. Vastsündinud, kes olid hüpotensiivsed gestatsioonivanuse kriteeriumite järgi, kuid kellel ei olnud kliiniliselt perfusioonihäiret, olid sama heade kaugtulemustega nagu normotensiivsed patsiendid. Ravitud hüpotensioon oli seotud ebasoodsa kaugtulemusega (Dempsey 2009)[2,3].

Mõiste "lubatud hüpotensioon" e. ingl. k. permissive hypotension – s.t. esineb hüpotensioon, kuid kudede perfusion ja oksügenisatsioon on hea. Süsteemse verevoolu ja vererõhu vahel enneaegsetel lastel on vähene korrelatsioon või see puudub; väga madal süsteemne perfusioon, šokk, võib esineda ka normaalse vererõhu korral. Vastupidi, enneaegsed vastsündinud, kelle vererõhk on keskmisest madalam, sageli ei ole neil kliinilisi või biokeemilisis šoki tunnuseid, eeldatavasti on neil adekvaatne kudede oksügenisatsioon ja tõenäoliselt ei vaja nad ravi, s.o. nn. „lubatud hüpotensioon". Kui süsteemne oksügenisatsioon halveneb, käivituvad kompensatoorsed mehhanismid, et tagada perfusioon ja oksügenisatsioon elutähtsates organites, nagu perifeerne vasokonstriktsioon, mis säilitab vererõhu (hüpotensioonita šokk). Dekompensatsioonifaasi iseloomustavad hüpotensiooniga kaasnev perfusioonihäire (hüpotensiooniga šokk), mis lõpuks võib viia ilma ravita tagasipöördumatute muutusteni (Dempsey 2009)[4].

Ei ole valideeritud kliinilist skooringsüsteemi, millega oleks võimalik diagnoosida šokki või süsteemse perfusiooni puudulikkust, mis on seotud ilmse madala vererõhuga enneaegsetel vastsündinutel.

Perfusiooni kliiniline hindamine on kergesti kasutatav kõigile, mõningaid kliinilisi ja biokeemilisi parameetreid saab kasutada n.ö. "voodiääres".

Perfusiooni hindamise kaudsed kliinilised ja biokeemilised parameetrid on:

pikenenud kapillaarse täitumise aeg (CRT - capillary refill time) – patoloogiline üle 4sek., nahajume, südamesagedus, vererõhk, diurees, liigutuste aktiivsus, happe-alus tasakaal, laktaadi näitajaid. Ükski nendest näitajatest ei ole isoleeritult spetsiifiline perfusiooni hindamiseks, paljud neist on subjektiivsed, nende korratavus on küsitav, kuid koos vererõhu näitajatega annavad paremat informatsiooni perfusioonist, täiendavad vererõhu näitude usaldusväärsust. (Dempsey 2007,2009,2014, Gale 2010, Miletin 2009, Hüpotensiooni ravijuhis 2011)[4,2,8,7,6]. Kõikide näitajate puhul ei saa kindlaid väärtusi paika panna. Näitajaid tuleks hinnata kompleksel, mitte üksikult kindlate väärtuste järgi. Vereringe kompleksek hindamiseks tuleks neid kasutada enneaegsete vastsündinute esmasel stabiliseerimisel (s.t. sünnitustoas kuni transpordini minekuni).

Kapillaarse täitumise aja väärtused (CRT) on ajaliste vastsündinute kohta, enneaegsetele vastsündinutele on nende kasutamine piiratud, Osborn kolleegidega näitasid uuringutes nõrka seost CRT ja süsteemse verevoolu vahel (Dempsey 2009, Miletin 2009)[2,6]. Kapillaarse täitumise aega mõõdetakse otsmikul, eelistatult sternumi keskosas, suurel varbal, standard tehnikaga (s.t. kerge surve avaldamine 5 sekundi jooksul, siis vabastada survest ja mõõta aeg, mis läheb värvuse taastumiseks). **Pikenenud kapillaarse täitumise aeg on >4sek.** (Miletin 2009)[8]. **Kapillarse täitumise aja (CRT) hindamine** (2):

1. Tsentraalne kapillaarse täitumise aeg varieerub laias ulatuses (kuni 4 sek.) normi piires vastsündinutel (grade B)
2. Perifeerne CRT ei ole kõlblik hemodünaamika hindamiseks vastsündinutel (grade B)
3. Tsentraalne CRT ≥4 sekundi võib näidata tunduvalt vähenenud organite verevoolu (grade B) [7].

Laktaadi määramine on informatiivne kudede oksügenisatsiooni näitaja [Nguyen HB 2004]. Seerumi laktaadi korduvad määramised on vajalikud. Laktaadi väärtusi on

analüüsitud enneaegsetel vastsündinutel mitmetes kliinilistes olukordades [Izraeli S, 1993], k.a. sepsis [Fizgerald MJ 1992] ja nekrootiline enterokoliit [Abubacker M 2003]. Esimese elupäeva laktaadi väärtused võivad prognoosida kaugtulemust [Groenendaal F 2003; Deshpande SA, Platt MP 1997]. Deshpande ja Platt näitasid uuringutes, et kaugtulemused on halvemad, kui kopsude kunstlikul ventilatsioonil oleval vastsündinul, gestatsioonivanusega 23-40 rasedusnädalat, laktaadi väärtus on püsivalt tõusnud. Suremus oli 57%, kui kaks laktaadi väärtust olid kõrgemad kui 5,6 mmol/l, mis viitab laktaadi määramise vajalikkusele (Dempsey 2009)[2].

Spetsiifilist seerumi laktaadi hindamise kriteeriumit hüpotensiivsetel vastsündinutel ei ole. Ainult üks varasem uuring on võrrelnud seerumi laktaadi ja perfusiooni hindamise seost. Wardle ja kolleegid ei leidnud perifeerse oksügenisatsiooni hindamisel laktaadi taseme erinevust hüpotensiivsetel ja normotensiivsetel enneaegsetel vastsündinutel [Wardle SP 1999] .

Prospektiivses vaatlus-kohortuuringus väga väiksetel enneaegsetel leiti, et laktaadi väärtus rohkem kui 4 mmol/l ja pikenenud kapillaarse täitumise aeg üle 4 sekundi jalal, annab positiivse ennustava väärtuse PPV (positive predictive value) 80% ja NPV 88% madala vena cava superior`i (*SVC flow*) voolu leidmiseks, mis rõhutab kliiniliste ja biokeemiliste parameetrite kombineerimise väärtust (Dempsey 2009, Miletin 2009)[2,6].

Südamesagedus varieerub palju seoses gestatsiooni- ja postnataalse vanusega, korreleerub hapniku tarbimisega, kuid kindlaid väärtusi südame funktsiooni hindamiseks ei ole avaldatud. **Diurees** on esimesel elupäeval madal ja varieeruv, kuid hea diurees on julgustav. Kõigi nende näitajate koos arvestamine lubab hinnata patsiendi tulemusnäitajaid [Guissani DA 2005; Dempsey EM 2005]. Oliguuria on organite vähenenud perfusiooni üks näitajatest.

Vererõhu mõõtmine: invasiivne vererõhu monitooring – kasutades perifeerset või nabaarteri-sisest kateerit, mille küljes on kalibreeritud andur; mitteinvasiivne vererõhu mõõtmine – valideeritud ostsillomeetriline mõõtmine (automatiseeritud ostsillomeetriline mansett, vererõhu mõõtmiseks jäsemetelt monitoriga) (Ibrahim 2008)[5]. Invasiivne vererõhu mõõtmine on kuldseks standardiks.

Käimas on uuring Hypotension in Preterm Infants Consortium (HIP), kuhu on kaasatud neonatoloogid, teadlased, farmakoloogid ja ravimitööstuse partnerid. HIP eesmärk on hinnata randomiseeritud kontrolluuringuna kahte strateegiat ja määratleda kõige sagedamini kasutatav inotroopse ravimi - dopamiini efektiivsus (EudraCT No. 2010-023988-17; Clinical Trial Registration No.: clinical trials.gov NCT01482559) (8).

Kasutatud ülevaated:

1. **Use of Antihypotensive Therapies in Extremely Preterm Infants** Batton B., Li L., Newman N.S., RN, Abhik D., Watterberg K.L., Yoder B.A., Roger G.F., Laughon M.M., Barbara J.S., Meurs K.P., Carlo W.A., Poindexter B.B., Bell E.F., Sánchez P.J., Ehrenkranz R.A., Goldberg R.N., Laptook A.R., Kennedy K.A., Frantz I.D., Shankaran S., Schibler K., Higgins R.D., Walsh M.C., Pediatrics 2013;Vol 131, Number 6, June:e1865–e1873.
2. **Evaluation and Treatment of Hypotension in the Preterm Infant** Dempsey E.M., Barrington K.J., Clin Perinatol 36, (2009) 75–85
3. **Permissive hypotension in the extremely low birthweight infant with signs of good perfusion**. Dempsey E.M., Hazzani F.A, Barrington K.J. Arch Dis Child Fetal Neonatal Ed 2009; 94:F241–F244. doi:10.1136/adc.2007.124263

4. **Treating hypotension in the preterm infant: when and with what: a critical and systematic review.** Dempsey E.M, Barrington K.J. Journal of Perinatology, 2007; 27:469–478 doi:10.1038/sj.jp.721177
5. **Hypotension in Preterm Infants** Review article, IBRAHIM H., INDIAN PEDIATRICS 2008, VOLUME 45, APRIL 17, 285-294.
6. **Bedside detection of low systemic flow in the very low birth weight infant on day 1 of life** J. Miletin & K. Pichova & E.M. Dempsey, Eur J Pediatrics, 2009; 168:809–813 DOI 10.1007/s00431-008-0840-9
7. Question 2 **IS CAPILLARY REFILL TIME A USEFUL MARKER OF HAEMODYNAMIC STATUS IN NEONATES?** Gale C, ArchDisChild, 2010; 95:395 397.doi:10.1136/adc.2010.186411
8. **Management of Hypotension in Preterm Infants (The HIP Trial): A Randomised Controlled Trial of Hypotension Management in Extremely Low Gestational Age Newborns** Dempsey E.M., Barrington K.J., Marlow N., O'Donnell C.P., Miletin J., Naulaers G., Cheung P.-Y., Corcoran D., Pons G., Stranak Z., D. Van Laere on behalf of the HIP Consortium Neonatology, 2014; 105:275–281 DOI:.1159/000357553

Ravijuhendid

Kokkuvõte ravijuhendites leiduvast

Soovitused vastsündinu hemodünaamika hindamiseks esmasel stabiliseerimisel olid leitavad kahes AGREE-ga hinnatud ravijuhendis.

1.The Management of Hypotension in the Very-Low-Birth-Weight Infant: Guideline for Practice, 2011, Endorsed by American Academy of Pediatrics

Madal süsteemne vererõhk (low systemic blood flow (LSBF)) on seisund, kui on vähenenud organite verevarustus, mis viib hapniku transpordi häireni elundites kuni šoki kujunemiseni. Väga väikese sünnikaaluga vastsündinutel ei ole teada vererõhu parameetrid, mis mõjutavad haigestumust, suremust ja nende kaugtulemust [*McClean CW et al 2008*]. Ei ole veenvaid tõendeid, et hüpotensiooni ravi vähendaks suremust ja neuroloogilist haigestumust, ühes uuringus leiti, et ravi võib olla seotud IVH tekkega (Synnes 2001). Hiljutistes retrospektiivsetes uuringutes "ravitud hüpotensioon" oli seotud haigestumuse ja kuulmislangusega väga väikestel enneaegsetel ning ebasoodsate kaugtulemustega (Hüpotensiooni ravijuhis 2011, Dempsey 2009) [2].

Neonataalses praktikas kasutatakse tavaliselt kahte vererõhu parameetrit – hüpotensiooniks loetakse kolmel esimesel elupäeval kas keskmist arteriaalset rõhku (MAP) alla 30 mmHg või MAP alla vastsündinu gestatsioonivanuse nädalates. Eksisteerivate tõendite järgi, üle 3 elupäeva, rohkem kui 90% VLBW 23-26 rasedusnädalal sündinud vastsündinutel on MAP üle 30 mmHG [*Nuntnarumit PY et al 1999*].

Vererõhu mõõtmine on ainult üks osa vastsündinu hemodünaamika hindamisest ja selleks, et saada ülevaade vererõhu kõrval ka süsteemsest verevoolust, süsteemsest vaskulaarsest resistentsusest ja verevoolu regulatsioonist organites, tuleb arvestada paljusid faktoreid: vena cava superior`i voolu (*SVC flow*), kopsuvereringe voolu, süsteemset vaskulaarset resistentsust, avatud arteriaalse juha voolu (*ductal flow*), parema vatsakese väljutusmahtu, müokardi ja teiste organite ebaküpsust, haiguse patofüsioloogiat, kudede oksügenisatsiooni, CO2 taset jne.[*Kluckow M et al 2001; Noori S et al 2009; Seri, I et al 2001*]. Enamus neist

parameetritest ei ole pidevalt ja kergesti mõõdetavad, kuid neid tuleks arvestada enne ravi alustamist.

Vastsündinu hemodünaamika hindamiseks hüpotensiooni ravi alustamisel väga väikestel enneaegsetel on kindlalt **soovitav kasutada kaudseid kliinilisi parameetreid organite vähenenud perfusioonist, mis täiendavad süsteemse verevoolu hindamist, milleks on: tõendid metaboolsest atsidoosist koos tõusnud seerumi laktaadi tasemega, võimalik südamesageduse tõus, kapillaaride täitumise aja pikenemine, diureesi muutused** (Hüpotensiooni ravijuhis 2011).

2. European Consensus Guidelines on the Management of Neonatal Respiratory Distress Syndrome in Preterm Infants – 2013 Update

Sweet D.G., Carnielli V., Greisen G., Hallman M., Ozek E., Plavka R., Saugstad O.D., Simeoni U., Speer C.P., Vento M., Halliday H.L. Neonatology, 2013; 103:353–368 DOI: 10.1159/000349928

Grades of recommendation: GRADE

A	At least one meta-analysis, systematic review or RCT rated as 1++ and directly applicable to the target population or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating consistency of results or Extrapolated evidence from studies such as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating consistency of results or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4 or Extrapolated evidence from studies rated as 2+

GRADE = Grading of recommendations assessment, development and evaluation [5]; RCT = randomized controlled trial.

Madal süsteemne verevool ja hüpotensiooni ravi on olulised võimaliku halva kaugtulemuse määrajad *[Osborne DA et al 2007, Fanaroff JM et al 2006]*. Enneaegsetel vastsündinutel ei ole need korrelatsioonis, eriti kolmel esimesel elupäeval *[Dempsey EM et al 2009, Kluckow M et al 1996]*. Aju verevoolu näitajad on saransed hüpotensiivsetel ja normotensiivsetel väga väikese sünnikaaluga enneaegsetel vastsündinutel *[Lightburn MH et al 2009]*. Ei ole kindlaks määratud, millised peaksid olema normaalsed aktsepteeritavad vererõhu näitajad, kuid paljude klinitsistide eesmärk on hoida keskmine arteriaalne vererõhk suurem/võrdne gestatsioonivanusega nädalates *[Cayabyab R et al 2009]*. Selleks, et hinnata süsteemset verevoolu ja hüpotensiooni ravi vajadust täpsemalt, tuleb kombineerida kliinilisi ja ehhokardiograafilisi näitajaid *[Fanaroff JM et al 2006, Dempsey EM et al 2009, Cayabyab R et al 2009]*.

Põhjuse väljaselgitamine on õige ravi määramise aluseks.

Ravijuhise soovitus on monitoorida vererõhku regulaarselt. Hüpotensiooni ravi rakendada, kui esineb kudede perfusiooni häire (LOE C).

Viited

Kokkuvõte (abstract või kokkuvõtlikum info)	**Viide kirjandusallikale**
Target Population Premature infants born at 1,500 grams or less and less than 3 postnatal days old **Recommendations and Grading Criteria** The following grading system was employed to rate the quality and strength of the evidence to support the practice recommendations: **Rating System for the Hierarchy of Evidence** **Level I:** Evidence from a systematic review or meta-analysis of all relevant randomized controlled trials (RCTs) or evidence-based clinical practice guidelines based on systematic reviews of RCTs **Level II:** Evidence obtained from at least one well-designed RCT **Level III:** Evidence obtained from well-designed controlled trials without randomization **Level IV:** Evidence from well-designed case-control and cohort studies **Level V:** Evidence from systematic reviews of descriptive and qualitative studies **Level VI:** Evidence from a single descriptive or qualitative study **Level VII:** Evidence from the opinion of authorities or reports of expert committees From *Evidence-Based Practice in Nursing and Healthcare: A Guide to Best Practice* (p. 10), by B. M. Melnyk & E. Fineout-Overholt, 2005, Philadelphia: Lippincott Williams and Wilkins. Copyright 2005 by Lippincott Williams and Wilkins (http://www.lww.com/). Reprinted with permission. *Hypotension*—Experts believe that three different levels of functional alteration in the VLBW infant can be used to refine the definition of *hypotension*: a loss of vital organ blood flow autoregulation, a loss of function, and a loss of tissue integrity (ischemic threshold) [McClean CW et al 2008]. However, many unanswered questions remain regarding the determination of the specific blood pressure values that indicate pathology in VLBW infants within each level. In addition, it is unclear how to determine the specific blood pressure parameters that affect morbidity, mortality, and long-term outcome in the VLBW infant [McClean CW et al 2008]. In general neonatal practice the two most common parameters used to define hypotension during the immediate transitional period are a blood pressure that falls below a mean arterial pressure (MAP) of 30 mm Hg or a MAP with a number lower than the infant's gestational age in weeks. These values will be used to define hypotension during the first 3 days of postnatal life because evidence exists that beyond this period, more than 90% of VLBW infants with gestational ages of 23–26 weeks will have a MAP greater than 30 [Nuntnarumit PY et al 1999].	**The Management of Hypotension in the Very-Low-Birth-Weight Infant: Guideline for Practice, 2011.** Endorsed by American Academy of Pediatrics

Very-low-birth-weight (VLBW) infant—a premature infant weighing less than 1,500 grams at birth.
Low systemic blood flow (LSBF)—the condition existing when a decreased amount of blood reaches systemic end organs, resulting in decreased oxygen delivery to the organs and the development of shock.

Practice Recommendation	Level of Evidence	Reference(s)
1. Hypotension in VLBW infants should be treated on the basis of the etiology of the hypotension whenever an etiology is known. **Rationale**: It is generally agreed by experts that adequate treatment of blood pressure requires identification of the primary factor leading to the hypotension.	VII	15, 16, 17
2. In general, the early use of volume expansion with normal saline, fresh frozen plasma, albumin, plasma substitute, or blood in VLBW infants with hypotension is not recommended. **Rationale**: Evidence that VLBW infants with hypotension benefit from volume expansion is insufficent, as is evidence to determine what type of volume expansion should be used in VLBW infants.[18,19] The majority of VLBW infants who are hypotensive are not hypovolemic and have normal circulating blood volume.[15,16]	I VII	18, 19 15, 16
3. In VLBW infants with evidence of placenta previa, abruption, blood loss from the umbilical cord, fetal anemia, or evidence of fetal-maternal transfusion, the administration of a volume expander such as normal saline, ringers lactate, or O Rh-negative blood may be used as an initial dose of 10 ml/kg given over 5–10 minutes. This dose may be repeated.[20] Albumin is not generally recommended for use as a volume expander in VLBW infants. **Rationale**: In VLBW infants with evidence of blood loss, the effective circulating blood volume may be decreased, which can result in hypotension. Volume expansion will restore normal intravascular volume, increase preload, and thus increase cardiac output in a hypovolemic baby.[20,21,22] Use of albumin is not generally recommended because of the increased risk of infection (it is a blood product); also, the cost of isotonic saline is approximately one-fifth the cost of 4.5% human albumin.[23]	VII	20, 21, 22, 23
4. Dopamine, carefully titrated to the optimum hemodynamic response, should be considered prior to dobutamine for treatment of hypotension alone in VLBW infants when the cause of hypotension is unknown. **Rationale**: Dopamine is more effective than dobutamine for treating hypotension in premature infants. Dopamine does not appear to affect the incidence of severe periventricular hemorrhage, periventricular leukomalacia, or tachycardia. *Cautious stepwise increases* in dopamine in hypotensive VLBW infants are not associated with an abnormal neurologic picture, combined adverse outcomes (death, cerebral palsy, or profound neurodevelopmental delay), or developmental delay.	I III	24 25, 26
5. In VLBW infants with hypotension and LSBF during the *first postnatal day* caused by the immature myocardium's inability to pump against the sudden increased peripheral resistance that occurs with the removal of the placenta (myocardial dysfunction is caused by the VLBW infant's decrease in cardiac output when faced with an increase in peripheral resistance) and vasoconstriction of the immature forebrain vasculature, dobutamine may be considered the initial treatment choice in improving blood pressure. If blood pressure decreases after beginning dobutamine, low-dose dopamine can be added to the treatment regimen. **Rationale**: Dobutamine has a direct positive inotropic effect and has a variable degree of peripheral vasodilatory response. Thus, in situations where the VLBW infant's cardiac output has been compromised by the sudden increased peripheral resistance caused by removal of the low resistance placenta, as happens after birth, experts believe that *cautious stepwise increases* in dobutamine may increase cardiac output by promoting systemic vasodilation and improving LSBF. However, *no evidence* that dobutamine promotes vasodilation in the 1-day-old VLBW infant exists. Use of dopamine, primarily at high doses, in these patients may further increase vasoconstriction and decrease systemic blood flow and thus decrease cardiac output.[28]	I VII	27 28

(continued)

6. If hypotension in the VLBW infant is related to evidence of infection, dopamine should be considered as the first-line treatment. If dopamine is not effective, treatment with epinephrine should be considered. **Rationale**: Hypotension related to infection is primarily caused by systemic vasodilation. Only in the late phase of sepsis is hypotension related to myocardial dysfunction. Therefore, hypotension in VLBW infants with probable infection should be treated with a vasopressor or intropic agent such as dopamine or epinephrine that will promote vasoconstriction as well as myocardial function.	VII	28, 29, 30
7. Epinephrine can be as effective as dopamine in increasing blood pressure in hypotensive VLBW infants, but knowledge about epinephrine's effect on systemic blood flow is limited. **Rationale**: Low-dose epinephrine has strong beta- and somewhat weaker alpha-adrenergic effects and produces an increase in cardiac output and blood pressure. *Cautious stepwise increases* in epinephrine in hypotensive VLBW infants are not associated with an abnormal neurologic picture, combined adverse outcomes (death, cerebral palsy, or profound neurodevelopmental delay), or developmental delay.	II	25, 28, 31, 32, 33
8. The use of hydrocortisone is as effective as dopamine in improving hypotension in VLBW infants, but data on the long-term safety of corticosteroids for this use are insufficient. Thus, its use should be reserved for infants with refractory hypotension. Hydrocortisone should *not* be used concurrently with indomethacin. When one is considering the use of hydrocortisone for treatment, it may be useful to obtain a baseline serum cortisol level; this may identify infants with low levels who will benefit from hydrocortisone treatment. **Rationale**: Hydrocortisone has been shown to improve hypotension, increase tissue perfusion, and prevent ischemic tissue injury. However, hydrocortisone's neurodevelopmental effects and long-term effects are unclear. Nor is it clear whether longer-term clinical outcomes are improved with the use of hydrocortisone. Low baseline serum cortisol levels may identify infants who will benefit from hydrocortisone treatment; one study demonstrated that infants with serum cortisol levels below the median who were treated with hydrocortisone had increased survival without bronchopulmonary dysplasia when compared to those who did not receive hydrocortisone.	I II V VI VII	34 35, 36, 37, 38 39 40 41, 42
9. A single dose of dexamethasone may increase blood pressure in hypotensive VLBW infants, but dexamethasone cannot be recommended because of its documented negative effect on neurodevelopmental outcomes if given during the first postnatal days. **Rationale**: Several studies using both long and short courses of dexamethasone with relatively high doses have demonstrated significant effects on central nervous system development. Because of these findings and the lack of information on the safety of a short-course, lower-dose dexamethasone for treatment of hypotension, it cannot be recommended for use at this time.	I II VII	34 43, 44, 45, 46 15
10. At present, no evidence supports the use of milrinone for the treatment of hypotension in VLBW infants. **Rationale**: A double-blinded randomized controlled trial comparing the effectiveness of milrinone versus placebo on LSBF in VLBW infants demonstrated that milrinone did not prevent LSBF in these infants. No adverse effects were demonstrated with milrinone.	II	47
11. Research to recommend the use of dopamine (or other vasopressor-inotropes) for the treatment of hypotension related to a patent ductus arteriosus (PDA) in VLBW infants is scant. **Rationale**: Only one observational prospective study has been conducted that suggested that dopamine increased pulmonary vascular resistance in VLBW infants with hypotension and PDA and thus increased blood pressure and systemic blood flow (SVC flow) by decreasing the left-to-right shunt.	VI VII	48 49

Potential Benefits and Harms

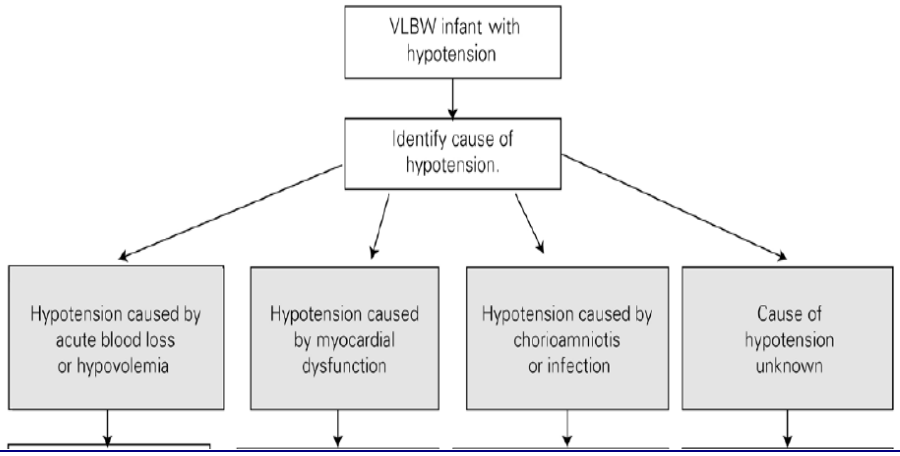
The primary goal of treating hypotension in VLBW infants is to maintain systemic blood flow, preserving end-organ perfusion and thus oxygen delivery to the tissues. The clinical emphasis is generally placed specifically on preserving cerebral blood flow and oxygen delivery *[Seri I et al 2001]*. Studies have correlated hypotension with LSBF, decreased cerebral blood flow, increased incidence of brain injury, and increased adverse neurodevelopmental outcome *[Miall-Allen VM et al 1987,Goldstein RF et al 1995, Osborne DA et al 2003, Hunt RW et al 2004]*. Intestinal injury due to decreased organ perfusion has also been a concern.

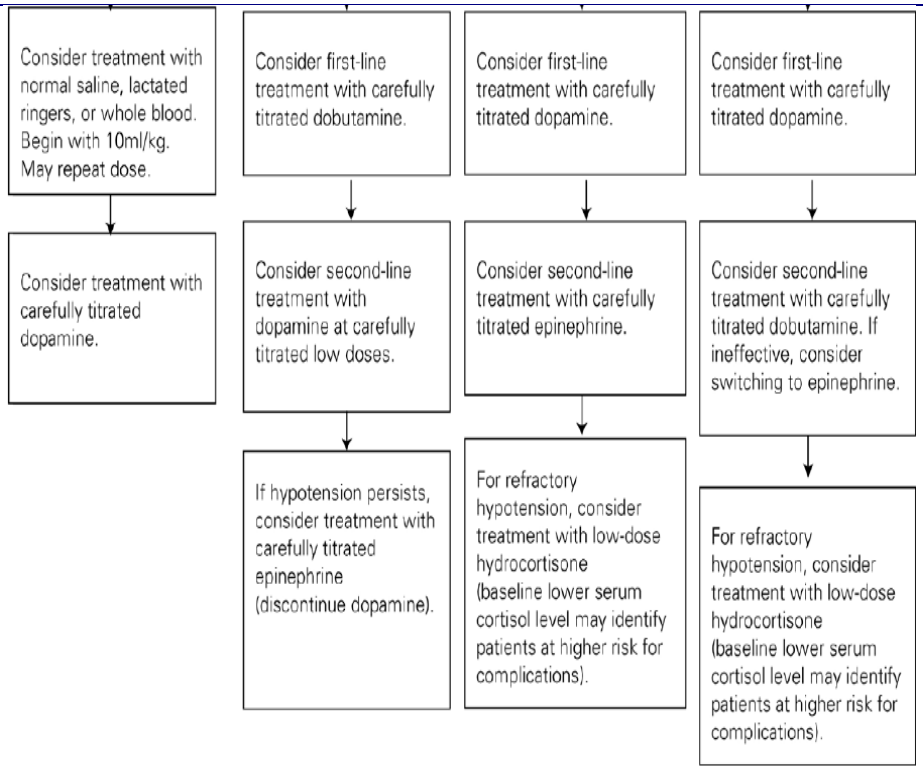
However, evidence exists that maintaining normal blood pressure may be only a part of the picture for the VLBW infant and that assessment of systemic blood flow requires more than measuring systemic blood pressure. The interaction among blood pressure, systemic blood flow, systemic vascular resistance, and blood flow regulation in vital and nonvital organs during transition to extrauterine life in the VLBW neonate is complex. Multiple factors—SVC flow, pulmonary blood flow, peripheral and pulmonary resistances, ductal flow, right ventricular output, immaturity of the myocardium, vital organ assignment, disease pathology, and tissue oxygen and carbon dioxide levels—are important to an understanding of the hemodynamics that affect VLBW infants and their well-being *[Kluckow M et al 2001, Noori S 2009, Seri I et al 2001]*. However, most of these parameters cannot be continually monitored at the patient's bedside in easily measured absoluute numbers. Monitoring LSBF is considered to be important for successfully managing the cardiovascular system in the VLBW infant *[Kluckow M et al 2001]*, but one must keep in mind the limitations of the available technologies and remain cognizant of the more complex picture when addressing these issues. We must be sure that we are not doing more harm than good. In fact, we have no convincing evidence that treating hypotension in VLBW infants decreases mortality and neurologic morbidity *[Osborne DA et al 2004]*, and findings from one study (albeit a study with limitations) imply that treatment may be associated with development of intraventricular hemorrhage *[Synnes AR et al 2001]*. Recent retrospective studies have also suggested that "treated hypotension" is associated with adverse outcomes. The results of one study suggested that treated hypotension was associated with morbidity and hearing loss in VLBW infants *[Fanaroff JM et al 2006]*. Another retrospective study demonstrated that treated hypotension in VLBW infants was associated with adverse outcomes *[Dempsey EM et al 2009]*. Although these retrospective findings are cautionary for treatment of hypotension and demonstrate the need for well-executed prospective studies that examine permissive hypotension and its consequences in this population, it is entirely unclear from these studies whether treatment has anything to do with the documented association. Indeed, it is possible that treatment of hypotension identifies a more vulnerable patient population or that treatment was initiated too late in the course of the clinical presentation or was ineffective, resulting in cerebral hypoperfusion and longterm neurodevelopmental disability. In summary, any treatment option should be carefully examined with these considerations in mind. When any vasoactive agent is used, careful titration of the drug is critical; only cautious stepwise increases should be made. In addition, clinicians need not wait more than approximately 3–5 minutes between the dose hanges while titrating the drug, as long as drug delivery with correct line priming is ensured and the infusion pump has been appropriately set up *[McClean CW et al 2008, Seri I et al 1993]*.	

It is imperative that one consider all parameters rather than just blood pressure before deciding on specific in for treating hypotension in VLBW infants. This guideline is based on the best evidence available through both neonatal research and consultation of experts on the subject. It suggests a conservative treatment approach that is logical, safe, and physiologically based. The insufficient fund of knowledge on transitional cardiovascular physiology in general and pathophysiology in particular makes establishment of strict guidelines on the treatment of hypotension in VLBW neonates impossible. This is also the reason that clinical studies addressing this question have been unable to provide the appropriate information and levels of evidence to guide management of neonatal hypotension in clinical practice *[Noori S et al 2009]*. What becomes clear when presenting the evidence is how much more we need to know.

Algorithm

Algorithm for Treatment of Hypotension in the VLBW Infant During the First 3 Days of Postnatal Life





We strongly encourage those who are considering treatment of hypotension to use other indirect clinical signs of decreased organ perfusion as adjuncts to assessing systemic blood flow in the attempt to define the need for blood pressure treatment in VLBW infants. These clinical signs include changes in urine output, evidence of metabolic acidosis with increased serum lactate levels, and possibly increased heart rate and capillary refill time [*Engle JR et al 2008*].

Table 1. Levels of evidence and grades of recommendation

Levels of evidence	
1++	High-quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews or RCTs with a low risk of bias
1–	Meta-analyses, systematic reviews or RCTs with a high risk of bias
2++	High-quality systematic reviews of case control or cohort studies High-quality case control or cohort studies with a very low risk of confounding bias
2+	High quality case control or cohort studies with a low risk of confounding bias
2–	Well-conducted case control or cohort studies with a high risk of confounding bias
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion
Grades of recommendation: GRADE	
A	At least one meta-analysis, systematic review or RCT rated as 1++ and directly applicable to the target population or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating consistency of results or Extrapolated evidence from studies such as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating consistency of results or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4 or Extrapolated evidence from studies rated as 2+

GRADE = Grading of recommendations assessment, development and evaluation [5]; RCT = randomized controlled trial.

Managing Blood Pressure, Perfusion and Patent Ductus Arteriosus

Low systemic blood flow and treatment for hypotension are important predictors of poor long-term outcome *[Osborne DA et al 2007, Fanaroff JM et al 2006]* . In preterm newborns blood pressure and systemic blood flow are not closely correlated, especially during the transitional circulation in the first 3 days of life *[Dempsey EM et al 2009, Kluckow M et al 1996]* . Cerebral blood flow measurements are similar in well hypotensive compared to normotensive extremely low birth weight infants *[Lightburn MH et al 2009]* . There is a lack of data to determine what normal acceptable blood pressure values should be but, as a guide, many clinicians aim to maintain the mean arterial pressure above the gestational age in weeks *[Cayabyab R et al 2009]* . There is a move to assess systemic blood flow more accurately using a combination of clinical examination and functional echocardiography to determine if low blood pressure is affecting tissue

European Consensus Guidelines on the Management of Neonatal Respiratory Distress Syndrome in Preterm Infants – 2013 Update

Sweet D.G., Carnielli V., Greisen G., Hallman M., Ozek E., Plavka R., Saugstad O.D., Simeoni U., Speer C.P., Vento M., Halliday H.L.

Neonatology, **2013**; 103:353–368 DOI: 10.1159/00034992

perfusion and thus help to determine if treatment for hypotension is *needed [Fanaroff JM et al 2006, Dempsey EM et al 2009, Cayabyab R et al 2009]*. Low systemic blood flow and hypotension during RDS may be related to hypovolemia, large left-to-right ductus or atrial shunts, or myocardial dysfunction. Knowing the cause can indicate the most appropriate treatment. Early hypovolemia can be minimized by delaying cord clamping. The practice of saline boluses has been questioned as the bolus is rapidly distributed to the extravascular space and may increase lung oedema *[Wyckoff M et al 2007]*. Volume expansion with 10–20 ml/kg of normal saline, rather than colloid, can be considered when hypovolemia has been confirmed by echocardiography or if the cause is not clearly established *[Osborn DA et al 2004, Wong W et al 1997]* . *Recommendations* (1) Treatment of arterial hypotension is recommended when it is confirmed by evidence of poor tissue perfusion (C). **Summary of recommendations (Tabel 4):** Blood pressure should be monitored regularly, aiming to maintain normal tissue perfusion, if necessary using inotropes.	
OBJECTIVE: To investigate the relationships among blood pressure (BP) values, antihypotensive therapies, and in-hospital outcomes to identify a BP threshold below which antihypotensive therapies may be beneficial. **METHODS:** Prospective observational study of infants 23 0/7 to 26 6/7 weeks' gestational age. Hourly BP values and antihypotensive therapy use in the first 24 hours were recorded. Low BP was investigated by using 15 definitions. Outcomes were examined by using regressioon analysis controlling for gestational age, the number of low BP values, and illness severity. **RESULTS:** Of 367 infants enrolled, 203 (55%) received at least 1 antihypotensive therapy. Treated infants were more likely to have low BP by any definition (P < .001), but for the 15 definitions of low BP investigated, therapy was not prescribed to 3% to 49% of infants with low BP and, paradoxically, was administered to 28% to 41% of infants without low BP. Treated infants were more likely than untreated infants to develop severe retinopathy of prematurity (15% vs 8%, P = .03) or severe intraventricular hemorrhage (22% vs 11%, P < .01) and less likely to survive (67% vs 78%, P = .02). However, with regressioon analysis, there were no significant differences between groups in survival or in-hospital morbidity rates. ***Methods*** BP values were obtained from an arterial catheter when available or by oscillography. Antihypotensive therapy was defined as receipt of a fluid bolus (at least 10 mL/kg of crystalloid), dopamine, dobutamine, epinephrine, hydrocortisone, vasopressin, or any blood product. For all analyses, 15 definitions of low BP were investigated: 1, 2, or ≥3 systolic, diastolic, or mean BP values less than or equal to the fifth percentile; 1, 2, or ≥3 mean arterial pressure (MAP; in mm Hg) values less than or equal to the infant's GA equivalent (in weeks); and 1, 2, or ≥3MAP values ≤25 mmHg. Low BP values were not necessarily	**Use of Antihypotensive Therapies in Extremely Preterm Infants** Batton B., Li L., Newman N.S., Abhik D., Watterberg K.L., Yoder B.A., Roger G.F., Laughon M.M., Barbara J.S., Meurs K.P., Carlo W.A., Poindexter B.B., Bell E.F., Sánchez P.J., Ehrenkranz R.A., Goldberg R.N., Laptook A.R., Kennedy K.A., Frantz I.D., Shankaran S., Schibler K., Higgins R.D., Walsh M.C. Pediatrics **2013**; Vol 131, Number 6, June:e1865–e1873.

consecutive. At each postnatal hour, BP percentiles were constructed for different populations (all infants, only infants who did not receive therapy, and at each specific GA) by using 2 sets of BP values (all BP values versus only invasive BP values). The fifth percentile was numerically similar (within 2 mm Hg) for all populations analyzed, and results were statistically similar irrespective of which construct was used to define the fifth percentile.

Results

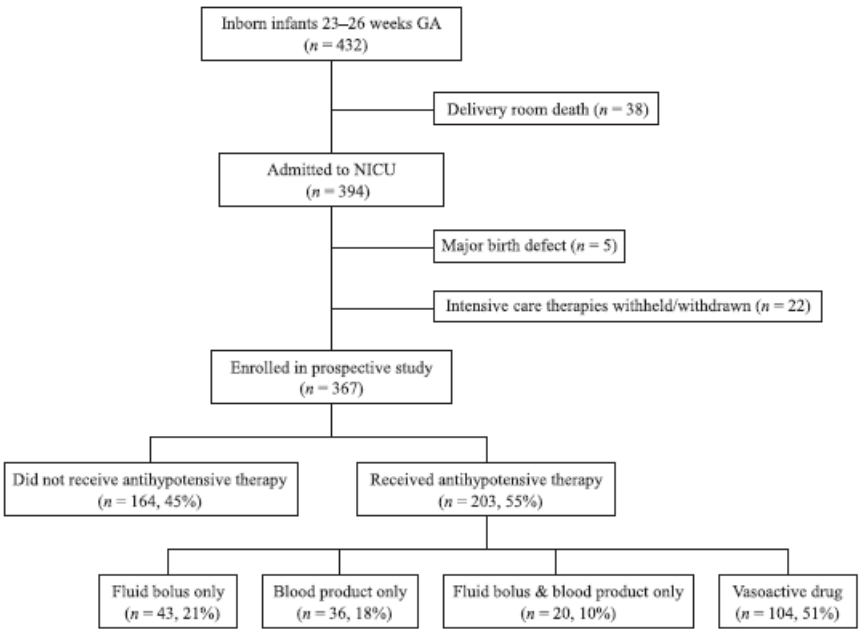


FIGURE 1
Extremely preterm infant study enrollment including classification by study group.

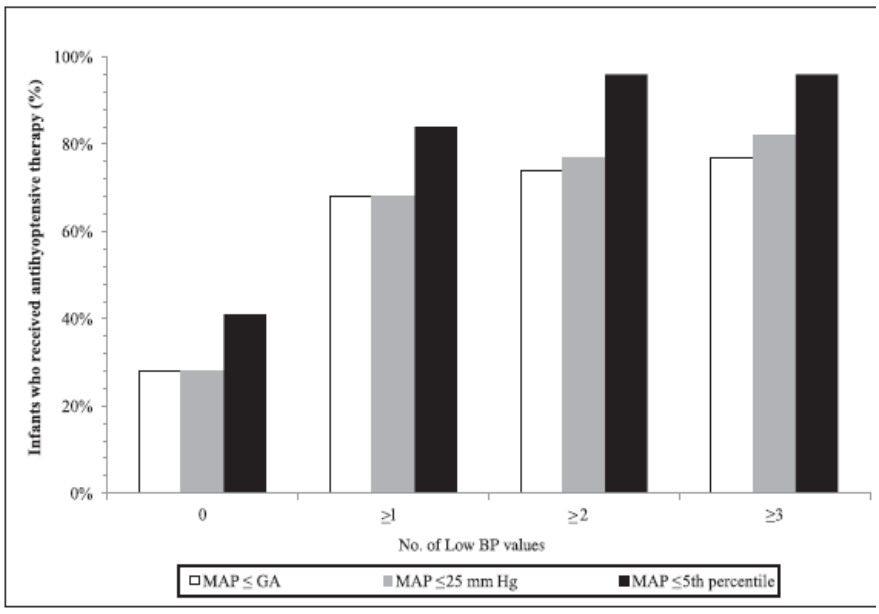


FIGURE 2
Percentage of infants with stated definition of low BP who received at ≥1 antihypotensive therapy.

TABLE 1 Baseline Characteristics for Infants Who Did or Did Not Receive Antihypotensive Therapy in the First 24 Hours

Initial Characteristic	No Therapy ($n = 164$)	Administered Therapy ($n = 203$)	*P* Value
Received maternal antibiotics, *n* (%)	126 (77)	160 (79)	.58
Received (any) prenatal steroids, *n* (%)	147 (90)	188 (93)	.31
Vaginal delivery, *n* (%)	53 (32)	68 (33)	.84
Multiple gestation, *n* (%)	39 (24)	63 (31)	.12
Male gender, *n* (%)	73 (45)	100 (49)	.36
Birth wt, g, mean ± SD	764 ± 161	698 ± 156	<.01
GA, weeks, mean ± SD	25.5 ± 0.9	25.1 ± 1.1	<.01
1-min Apgar ≤3, *n* (%)	70 (43)	122 (60)	<.01
5-min Apgar ≤5, *n* (%)	47 (29)	80 (39)	.03
DR chest compressions, *n* (%)	13 (8)	25 (12)	.17
First hematocrit <30%, *n* (%)	8 (5)	38 (19)	<.01
Positive initial blood culture, *n* (%)	—	8 (4)	.01
(Any) pH <7.10, *n* (%)	5 (3)	27 (13)	<.01

DR, delivery room.

TABLE 2 In-hospital Outcomes for Infants Who Did or Did Not Receive Antihypotensive Therapy in the First 24 Hours

In-hospital Outcomes	No Therapy ($n = 164$)	Administered Therapy ($n = 203$)	*P* Value
Necrotizing enterocolitis requiring surgery, *n* (%)	11 (7)	16 (8)	.92
Bronchopulmonary dysplasia, *n* (%)	75 (46)	92 (45)	.26
Cystic periventricular leukomalacia, *n* (%)	7 (4)	11 (5)	.60
Intervention for ROP, *n* (%)	13 (8)	31 (15)	.03
(Any) IVH, *n* (%)	43 (26)	83 (41)	<.01
Grade 3/4 IVH, *n* (%)	18 (11)	44 (22)	<.01
Survived 24 h, *n* (%)	156 (95)	186 (92)	.19
Survived ≥1 week, *n* (%)	146 (89)	174 (86)	.20
Survived to hospital discharge, *n* (%)	128 (78)	137 (67)	.02
Morbidity-free survival,[a] *n* (%)	24 (15)	11 (5)	<.01

[a] Morbidities: necrotizing enterocolitis, ROP, bronchopulmonary dysplasia, grade 3 or 4 IVH, or periventricular leukomalacia.

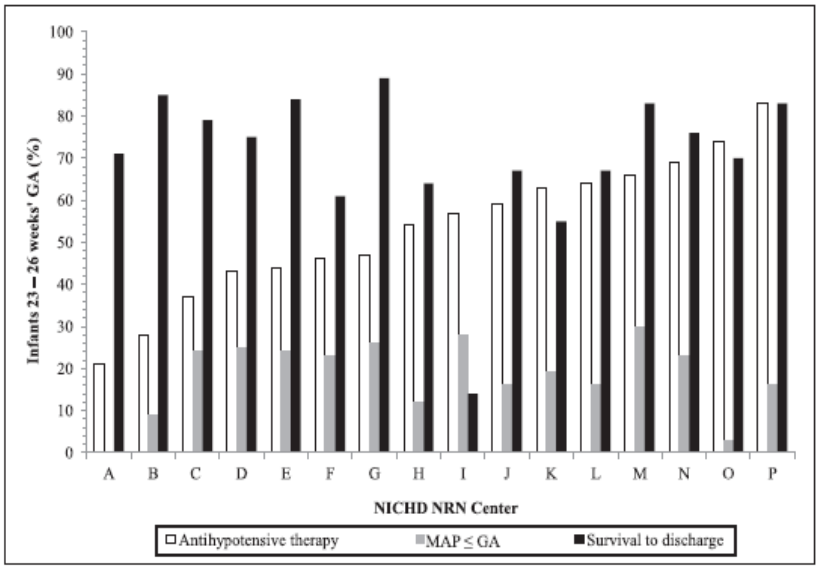


FIGURE 3
Center variation in the rate of antihypotensive therapy administration, frequency of low BP, and incidence of hospital survival.

Discussion

Other studies compared outcomes between infants with low BP who received an antihypotensive therapy and those who did not *[Batton B et al 2007, Logan JW et al 2011, Batton B 2009, Dempsey EM et al*

2009]. In those studies, treatment was associated with similar or worse infant outcomes when compared with untreated infants, but no study identified a definition of low BP for which treatment improved outcomes. Neither the current study nor others support the routine use of any antihypotensive therapy for any of the current definitions of low BP in extremely preterm infants *[Dempsey EM et al 2007, Laughon M et al 2007, Batton B et al 2007, Fanaroff JM et al 2006, Ewer AK et al 2003, Logan JW et al 2011, Batton B et al 2009, Dempsey EM et al 2009, Dempsey EM et al 2006, Bonestroo H et al 2011]*. Multiple definitions of low BP were investigated because there is not an accepted definition of hypotension in this population.

Although an MAP less than or equal to the infant's GA is the most common definition used *[Dempsey EM et al 2006]*,it is not evidence based and was first suggested in a policy statement on the management of respiratory distress syndrome *[Joint Working Party of British Association of Perinatal Medicine and the Research U nit of the Royal College Physicians 1922]*. However, infants with perceived low BP usually have adequate perfusion, *[Dempsey EM et al 2009, Bonestroo H et al 2011, Garner R 2013, Giliberti P 2010]* and the benefit of treatment has not been established for these infants. In this situation, therapies to increase BP appear also to be used to try to prevent or improve undocumented organ hypoperfusion, primarily cerebral blood flow *[Garner R et al 2013, Giliberti P et al 2010]*.

This approach is challenging because BP may not correlate with perfusion *[Garner R et al 2013, Giliberti P et al 2010, El-Khuffash AF et al 2008, Cayabyab R et Al 2009]*; infants with low BP may have adequate cerebral blood flow *[Bonestroo H et al 2011,Giliberti P et al 2010, Gilmore MM 2011, Tyszczuk L et al 1998]*, vasoactive drugs do not always increase cerebral perfusion [*Bonestroo H et al 2011, Garner R et al 2013]* and have not improved outcomes *[Osborne DA et al 2007]*, and treatment of low BP has been associated with similar or worse rates of intracranial abnormalities and impaired neurodevelopment versus matched untreated infants *Laughon M et al 2007, Batton B et al 2007, Fanaroff JM et al 2006,* Logan JW et al 2011, *Batton B et al 2009, Dempsey EM 2009]*.

CONCLUSIONS:

A numeric cutoff for deciding when to administer antihypotensive therapies, such as an MAP less than or equal to the infant's GA, is not evidence based and cannot be recommended. Until there are data to suggest otherwise, antihypotensive therapy should be used cautiously for these infants because treatment of low BP is associated with similar

or worse infant outcomes without evidence of benefit *[Batton B et al 2007, Logan JW et al 2011, Batton B et al 2009, Dempsey EM et al 2009]*.

Factors other than BP contributed to the decision to use antihypotensive therapies. Infant outcomes were not improved with antihypotensive therapy for any of the 15 definitions of low BP investigated.

The current review addresses issues regarding cardiovascular support in preterm infants: (1) definition of hypotension and shock in the preterm infant (2) clinical assessment of hypotension and shock (3) the short- and longterm consequences of hypotension (4) the therapeutic options available The definition of hypotension in the preterm infant is contentious. Hypotension could be defined as a ‘‘statistically low blood pressure.’’ Many normative blood pressure reference ranges exist based on birth weight, gestational age, and postnatal age criteria [*Lee J 1999; Spinazzola RM 1991; Watkins AM 1989; Versmold HT 1981; Hegyi T 1994, 1996;*]. The most popular criterion for diagnosing hypotension [*Dempsey EM 2006*] seems to be the Joint Working Group of the British Association of Perinatal Medicine [*Report of Working Group of the British Association of Perinatal Medicine and Neonatal Nurses Association on categories of babies requiring neonatal care. Arch Dis Child 1992;67(7 Spec No):868–9.*] recommendation that the mean arterial blood pressure in millimeters of mercury should be maintained at or greater than the mean gestational age in weeks. Despite a complete lack of published evidence to support this recommendation, it has been used as the primary entry criterion by several recent randomized therapeutic intervention trials [*Pellicer A 2005; Ng PC 2006*]. The question of how to define what is a ‘‘normal’’ blood pressure is difficult. It may be preferable to define hypotension by a blood pressure value lower than which there is a statistically increased risk for adverse outcome (ie, ‘‘unsafe blood pressure’’) if such a threshold exists and can be defined. The authors attempted to answer this question in a large database from very low birth weight (VLBW) infants and identified a statistically worse outcome with decreasing mean blood pressure thresholds. The incidence of adverse outcome (defined as grade 3 or 4 intraventricular hemorrhage [IVH]) increased from 21% to 31% when the definition of hypotension was reduced from 20 to 15 mm Hg in all patients less than 28 weeks of age. These definitions (20 and 15 mm Hg) accounted for only 7.1% and 1.2%, respectively, of the overall population of infants less than 28 weeks of age, however[*Barrington KJ 2002*]. When less extreme definitions of hypotension were applied, the increase in risk for severe IVH associated with hypotension was small. Even if we could define a threshold lower than which there is an increased chance of adverse outcome, this does not necessarily mean that intervention is going to result in improved outcome at such a value. There is little or no correlation between systemic blood flow and blood pressure in the preterm infant; extremely low systemic perfusion, shock, can occur with normal blood pressure. Conversely, preterm infants with blood pressure lower than average often have no biochemical or clinical signs of shock, presumably have adequate tissue oxygen delivery, and probably do not require treatment. We	**Evaluation and Treatment of Hypotension in the Preterm Infant** Dempsey E.M., Barrington K.J. Clin Perinatol 36 (**2009**) 75–85

have called this approach ‘‘permissive hypotension’’ [*Osborn D 2004*].

When systemic oxygen delivery decreases, there are several initial compensatory responses that occur to maintain perfusion and oxygen delivery to the most vital organs, including peripheral vasoconstriction, which maintains blood pressure (ie, shock without hypotension). Progression to the uncompensated phase is characterized by signs of poor perfusion accompanied by low blood pressure (ie, shock with hypotension), ultimately leading to the irreversible stage if appropriate therapy is not instituted. In contrast to the permissive hypotension approach mentioned previously, intervention to improve perfusion may be warranted in infants with shock despite normal blood pressure.

RECOGNITION OF HYPOTENSION AND SHOCK IN THE PRETERM INFANT

Clinical Signs

Bedside evaluation includes assessment of capillary refill time, color, heart rate, blood pressure, and urine output. None of these parameters in isolation is specific in identifying poor perfusion. Capillary refill time values exist for the term neonate, [*Raju NV 1999; Strozik KS 1997*] but there are limited data on capillary refill times in the preterm neonate[*Osborn D 2004; Wodey E 1998*].Osborn and colleagues showed a weak association between capillary refill time and systemic blood flow. Wodey and colleagues have shown a significant relation between cardiac index and capillary refill time in preterm neonates. The authors recently confirmed a limited relation between capillary refill values obtained in the forehead, sternum, and foot and simultaneously obtained superior vena cava (SVC) flow measurements [*Miletin J 2008*].

The relation between skin color and illness severity in the newborn has been evaluated using an objective measurement tool [*De Felice C 2002*].

Heart rates are extremely variable, vary with gestational and postnatal age, and correlate with oxygen consumption; however, neither absolute heart rate nor trend analysis of heart rate is validated as a way to assess cardiac function. Urine output is low and variable in the first 24 hours; however, good urine output is somewhat reassuring.

Although the positive predictive value (PPV) of each of these individual measures for identifying poor perfusion is unknown and likely to be low, it does seem that clinical assessment using a combination of signs allows one to identify patients with poor outcomes [*Guissani DA 2005; Dempsey EM 2005*].

Normal values for central venous pressure (CVP) in preterm infants have a wide range (2.8–13.9 mm Hg) [*Trevor Inglis GD 2007*], and there are numerous technical difficulties in obtaining CVP measurements. It is unclear if CVP correlates with circulating blood volume in the preterm infant; in any case, most preterm infants with lower blood pressure in the first few days are not hypovolemic. Thus,

CVP monitoring is of limited use in the NICU [*Skinner JR1992*].

Serum Lactate Values

Serial lactate measurements are useful in critically ill adults as a manifestation of poor tissue oxygen delivery [*Nguyen HB 2004*].Lactate values have been analyzed in several clinical situations in the preterm infant [*Izraeli S, 1993*], including sepsis [*Fizgerald MJ 1992*] and necrotizing enterocolitisv [*Abubacker M 2003*]. Values obtained during the first day of postnatal life can predict outcome [*Groenendaal F 2003; Deshpande SA, Platt MP 1997*]. Deshpande and Platt showed a worse outcome when lactate concentrations remained persistently elevated in sick ventilated newborns (23–40 weeks of gestation). Mortality was 57% if two lactate values were greater than 5.6 mmol/L, highlighting the importance of serial lactate assessments. Groenendaal and colleagues estimated the PPV and negative predictive value (NPV) of arterial lactate within 3 hours after birth in a cohort of preterm babies and found that with a cutoff value of 5.7 mmol/L, the PPV was 0.47 and NPV was 0.92 for a combined adverse outcome (death or poor neurodevelopmental outcome).

Data are limited on the use of serum lactate values specifically in hypotensive newborns. Only one previous study has evaluated the role of lactate in assessment of perfusion. Wardle and colleagues [*Wardle SP 1999*], in an assessment of peripheral oxygenation, found no difference in lactate levels between normotensive and hypotensive preterm infants.

In the authors' cohort of VLBW infants, they identified a weak negative correlation between lactate values and SVC flow. A combined lactate value of more than 4 mmol and prolonged capillary refill times of more than 4 seconds in the foot resulted in a PPV of 80% and a NPV of 88% for identifying low SVC flow, highlighting the value of combining clinical and biochemical parameters [*Miletin J, Dempsei EM 2008*].

SHOULD WE WORRY ABOUT HYPOTENSION?

The authors recently performed a systematic review to determine if there was a blood pressure threshold that accurately discriminated between preterm infants with a good outcome and those with an adverse outcome [*Dempsey EM 2007*]. They identified 18 studies in total, none of which were methodologically robust. The overall assessment of the data was that there is some association between having a lower blood pressure and häving a worse outcome; however, there are several potential confounding factors that preclude the elucidation of strong inferences from this association. The definition of hypotension varied substantially across the studies. One definition that has been used is a single mean blood pressure value less than 30mmHg [*Bada HS 1990*]. Such a definition may result in an artifactual association between hypotension and adverse outcome because the more immature babies, at greatest risk for IVH, are much more likely to be hypotensive by this rule.

The authors identified four studies that met the greatest proportion of their inclusion criteria [*Watkins AM 1998; Barrington KJ 2002; Bada*

HS 1990; Cunningham S 1999; Miall-Allen VM 1987]. Using continuous invasive blood pressure monitoring, Miall-Allen and colleagues identified an excess of IVH in preterm newborns with a mean blood pressure less than 30 mm Hg. Bada and colleagues showed that infants who developed moderate to severe IVH had lower blood pressure values for their postnatal ages than matched control infants who did not develop IVH. Watkins and colleagues, having taken postnatal age and birth weight into account, identified an association between a lower blood pressure (less than tenth percentile from self-constructed tables) and the frequency of severe IVH. The exact timing and duration of hypotension were not taken into account. Each of these studies was confounded by the fact that pressors were used and not accounted for in the analyses. More recently, Cunningham and colleagues found no association between the development of severe IVH and a prolonged period with a mean blood pressure less than gestational age in weeks. Data collected from the Canadian Neonatal Network have shown that those infants who had a lowest blood pressure less than their gestational age, or a blood pressure less than the tenth percentile using Watkins' criteria, were statistically slightly more likely to have severe IVH. This minor increase in risk was no longer apparent when pressor use was accounted for, however. Infants in the database who were not hypotensive and yet received inotropes were more likely to have a worse outcome than hypotensive patients who had not received such treatment. This finding could be interpreted in many different ways, one of which is that the adverse outcomes attributed in the past to hypotension are actually caused by the treatment of hypotension. An alternative explanation is as follows: physicians sometimes give cardiovascular support to infants who are unwell and poorly perfused despite an acceptable blood pressure (compensated shock), and such infants do poorly despite treatment. In contrast, the authors sometimes do not treat infants who have a statistically lower blood pressure but who appear to be well perfused, and such infants do well. Either of these explanations calls into question the common practice of routinely treating infants according to simplistic blood pressure thresholds.

SUMMARY

The definition and subsequent appropriate treatment of hypotension and the clinical diagnosis of shock remain elusive, as evidenced by the continued wide variation in practices across NICUs [Laughton M 2007]. Currently, many infants receive potentially toxic therapies based solely on simplistic criteria, such as a mean blood pressure less than the gestational age in weeks, in the absence of any evidence that such an approach is beneficial. An approach to treatment that includes blood pressure values but also clinical signs and biochemical values before deciding to initiate therapy markedly reduces the number of infants who receive therapy and is associated with good outcomes [*Dempsey EM 2005; Batton B 2007*]. Good clinical practice requires a careful assessment of the risks and benefits of an intervention before starting it. The available evidence suggests that an infant who is clinically well perfused despite a numerically low blood pressure is at

low risk and may not benefit from intervention. The frequency of treatment can be reduced by a clinically selective approach to as few as 11% of VLBW infants [*Dempsey EM 2005*] with no evidence of averse results. It is incumbent on those promoting a more interventionist approach to perform the requisite randomized controlled trials to prove that clinical outcomes are improved.	
ABSTRACT Introduction: Many practitioners routinely treat infants whose mean arterial blood pressure in mm Hg is less than their gestational age in weeks (GA). **Objective:** To assess the effectiveness of utilising a combined approach of clinical signs, metabolic acidosis and absolute blood pressure (BP) values when deciding to treat hypotension in the extremely low birthweight (ELBW) infant. **Methods:** Retrospective cohort study of all live born ELBW infants admitted to our neonatal intensive care unit over a 4-year period. Patients were grouped as either normotensive (BP never less than GA), hypotensive and not treated (BP,GA but signs of good perfusion; we termed this permissive hypotension) and hypotensive treated (BP,GA with signs of poor perfusion). **Results:** 118 patients were admitted during this period. Blood pressure data were available on 108 patients. 53% of patients were hypotensive (mean BP in mm Hg less than GA in weeks). Treated patients had lower birth weight and GA, and significantly lower blood pressure at 6, 12, 18 and 24 h. Normotensive patients and patients designated as having permissive hypotension had similar outcomes. Mean blood pressure in the permissive group increased from 26 mm Hg at 6 h to 31 mm Hg at 24 h. In a logistic regression model, treated hypotension is independently associated with mortality, odds ratio 8.0 (95% CI 2.3 to 28, p,0.001). **Conclusions:** Blood pressure spontaneously improves in ELBW infants during the first 24 h. Infants hypotensive on GA criteria but with clinical evidence of good perfusion had as good an outcome as normotensive patients. Treated low blood pressure was associated with adverse outcome. Global assessment of cardiovascular status includes assessment of other easily evaluable physical findings including capillary refill, skin colour, heart rate, urine output, level of activity and biochemical findings, in particular the degree of acidosis. Although this assessment of the adequacy of end organ perfusion is crude and not infallible, and each finding taken in isolation may be a poor indicator of perfusion, together they may provide more information than absolute blood pressure values alone. There is no evidence that attempts to achieve a ‘‘normal’’ blood pressure based on absolute reference values will improve outcomes, and the therapies available may be potentially toxic or *dangerous [De Zegher et al 1993, Valvede E et al 2006, Lopez SL 1997]*. We have consistently relied upon the assessment of clinical signs and degree of acidosis, in addition to absolute blood pressure values, before intervening in the management of low blood pressure states.	**Permissive hypotension in the extremely low birthweight infant with signs of good perfusion** Dempsey E.M., Hazzani F.A., Barrington K.J. Arch Dis Child Fetal Neonatal Ed **2009;** 94:F241–F244. doi:10.1136/adc.2007.124263

We evaluated this approach in the ELBW infant in the first 72 h of life. We hypothesised that patients with a blood pressure less than gestational age but who had evidence of good tissue perfusion and were not treated (permissive hypotension) had as good an outcome as patients with a lowest recorded blood pressure greater than gestational age. A secondary hypothesis was that infants who received therapy for low blood pressure had worse outcomes than those with low blood pressure but without symptoms.

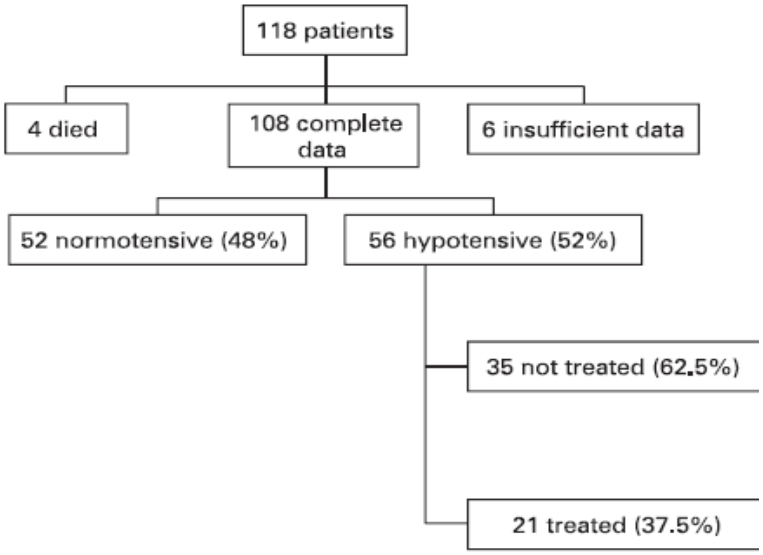


Figure 1 Flow diagram showing distribution of patients according to diagnosis and treatment of hypotension.

The decision to start any agent was made by the attending physician and was always based on a combination of absoluute mean blood pressure values, clinical signs suggesting poor tissue perfusion (including colour, heart rate, capillary refill and urine output), and absolute and temporal change in acidosis. Patients with a blood pressure less than gestational age are started on inotropic agents if they have signs of poor tissue perfusion. We therefore grouped our cohort as follows: either normotensive (BP never less than GA), hypotensive and not treated (BP,GA but signs of good perfusion; we defined this as permissive hypotension), hypotensive treated (BP,GA with signs of poor perfusion) and hypotensive infants whose only intervention was a blood transfusion as they also had a low haemoglobin concentration.

Table 1 Description of included patients

	Normotensive (n = 52)	Permissive hypotension (n = 34)	Treated hypotension (n = 18)	Hypotension, transfusion only (n = 4)
Birth weight (g), mean (SD)	828 (144)†	742 (131)	728 (149)	701 (44)
Gestation (weeks), mean (SD)	26.6 (1.6)	26.1 (1.6)	25.2 (1.62)*	24.0 (0.5)
CRIB II score, mean (range)	11 (7–18)	11 (8–16)	15 (9–16)*	15 (10–20)
BP at 6 h (mm Hg), mean (range)	32 (25–49)†	26 (16–42)	22 (14–34)*	19 (17–23)
BP at 12 h (mm Hg), mean (range)	34 (27–72)†	27 (17–35)	22 (12–32)*	21 (12–25)
BP at 18 h (mm Hg), mean (range)	33 (26–65)†	30 (20–37)	24 (13–33)*	23 (13–29)
BP at 24 h (mm Hg), mean (range)	35 (25–54)†	31 (22–41)	28 (16–36)*	25 (16–31)
Antenatal steroid	71%	82%	65%	50%
Vaginal delivery	35%	31%	32%	50%
RDS	76%†	91%	100%	100%
PDA	58%†	83%	37%	67%
NEC	4 (8%)	3 (9%)	2 (11%)	2 (50%)
Surgical NEC	1	1	1	0
Isolated GI perforation	2	0	1	0
Cystic PVL	1	0	0	0
IVH 3–4	2	4	5	2
Mortality	10	4	13*	2
Survival without severe IVH, cystic PVL, surgical NEC or GI perforation, n (%)	40 (77%)	26 (76%)	4 (22%)*	1 (25%)

BP, blood pressure; CRIB II, clinical risk index for babies; GI, gastrointestinal; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia; RDS, respiratory distress syndrome.
*Significantly different to the permissive hypotension and normotensive groups; †Significantly different to the permissive hypotension and treated hypotension groups.

This study addresses the role of clinical assessment of end organ perfusion when initiating treatment of hypotension, defined as blood pressure less than GA, in the ELBW infant during the first 72 h of life. Short-term outcome in patients who were hypotensive but had evidence of good perfusion was as good as in patients who were normotensive. This highlights a number of points. Firstly, absolute blood pressure values are only one indicator of circulatory status. Secondly, it confirms that a mean blood pressure less than gestational age in weeks alone is not a predictor of poor outcome. Thirdly, global assessment of cardiovascular status and intervention for hypotension restricted to infants with poor perfusion may be associated with good clinical outcomes and should be further evaluated. Clinical signs are by nature subjective and may be variably assessed. Their reproducibility may also be questionable. Evidence in relation to **the role of capillary refill** times in assessing end organ blood flow in the neonate is conflicting *[LeFlore et al 2005, Wodey et al 1998]*. Values exist for the term neonate *[LeFlore et al 2005]*, but there are limited data on capillary refill times in the preterm infant *[Wodey et al 1998]*. Osborn et al have also shown that there is a weak relationship between capillary filling and superior vena cava flow *[Osborna et al 2004]*. Because the normal urine output for an ELBW infant in the first 24 h is already very low, it is difficult to define low output. However, the presence of good urine output is reassuring. Previous investigations of the base deficit in ELBW infants have shown a correlation with poor outcome. **Serum lactate** measurements are probably preferable *[Desphande et al 1997]*, but were not routinely recorded in our infants. **Currently, no validated clinical scoring system is available**

to guide intervention in hypotensive infants. However, inclusion of these factors in decision making appears to decrease the number of infants who receive treatment without putting them at increased risk. In summary, a blood pressure less than the gestational age does not necessarily need to be treated. We observed good outcomes in hypotensive infants with good clinical perfusion who were carefully observed rather than treated.	

A very large proportion of extremely preterm infants receive treatments for hypotension. There are, however, marked variations in indications for treatment, and in the interventions used, between neonatal intensive care units and between neonatologists.

Methods: We performed systematic reviews of the literature in order to determine which preterm infants may benefit from treatment with interventions to elevate blood pressure (BP), and which interventions improve clinically important outcomes.

Results: Our review was not able to define a threshold BP that was significantly predictive of a poor outcome, nor whether any interventions for hypotensive infants improved outcomes, nor which interventions were more likely to be beneficial.

Conclusions: There is a distinct lack of prospective research of this issue, which prevents good clinical care. It is possible that a simple BP threshold that indicates the need for therapy does not exist, and other factors, such as the clinical status or systemic blood flow measurements, may be much more informative. Such a paradigm shift will also require careful prospective study.
Journal of Perinatology (2007) **27**, 469–478; doi:10.1038/sj.jp.7211774

Keywords: hypotension; preterm infant; systematic review; inotropes; fluid boluses

The objectives of this review were to determine if there exists sufficient evidence to determine which preterm infants may benefit from interventions to elevate BP, and which interventions improve clinically important outcomes. **These objectives created three questions:**

(1) Is there a defined BP threshold, or other clinical characteristics in preterm infants, which accurately identify those at risk for a poor outcome?

(2) Is there evidence that infants with hypotension (either as defined in #1 or arbitrarily) may have improved clinical outcomes if they receive intervention?

(3) Is there evidence regarding which interventions are most effective?

Treating hypotension in the preterm infant: when and with what: a critical and systematic review.

Dempsey E.M, Barrington K.J.

Journal of Perinatology **2007**; 27:469–478 doi:10.1038/sj.jp.7211177

Table 1 Description of studies reporting on the association between blood pressure and cerebral injury in the preterm infant

Study	*Patients*	*Prospective?*	*Hypotension definition*	*Study design*	*Outcome*	*Limitations*
Weindling *et al.* (1985)[17]	$N=86$ (<1500 g or <34 weeks)	Y	BP<30 mm Hg or received plasma because was clinically shocked	Cohort study	No significant association between hypotension and IVH	18% of eligible babies not studied, single BP threshold for all infants
Miall-Allen *et al.* (1987)[14]	$N=33$ (<31 weeks 700–1700 g)	Y	BP<30 mm Hg	Cohort study, masked ultrasounds	Increased IVH in hypotensive infants	Small sample size, single BP threshold for all infants
de Vries *et al.* (1988)[18]	$N=51$ (<34 weeks)	N	SBP <40 requiring colloid or dopamine	Case control	Increased PVL in hypotensive infants	Single BP threshold for all infants
Trounce and Shaw (1988)[19]	$N=200$ (<1501 g)	Y	Proportion of time with systolic <25, <35, <45, <55 mm Hg	Cohort study	IVH associated with duration of systolic >55 mm Hg	Blood pressures obtained in only 113 infants. Same BP thresholds for all infants
Watkins *et al.* (1989)[8]	$N=131$ (<1500 g)	N	Self-defined normals tenth percentile	Cohort study	Increased IVH in infants with ≥two readings below tenth percentile	
Bada *et al.* (1990)[15]	$N=100$ (<1500 g)	Y	Self-defined normals	Cohort Study	Increased IVH in hypotensive infants	
Low *et al.* (1992)[20]	$N=130$ (<34 weeks)	Y	95% confidence interval from previous study of 20 babies <1500 g	Cohort study	Increased cerebral lesions (IVH, ventriculomegaly, parenchymal lesions) in hypotensive infants	Used single BP standard for all infants <1500 g
Bejar *et al.* (1992)[21]	$N=$ 127 (<36 weeks)	N	Not defined	Cohort study	Not associated with white matter injury	
Gronlund *et al.* (1994)[22]	$N=42$ (<36 weeks, birthweight 1070–3720 g)	Y	Not defined	Cohort study	Increased IVH with elevated diastolic, mean and systolic blood pressures	Small sample size, three measurements of BP during the first 24 h.
Goldstein *et al.* (1995)[23]	$N=158$ (<1500 g)	N	<750 g systolic<35 mm Hg, 750–1500 g systolic <40 mm Hg	Cohort study	Increased adverse outcome (MDI, PDI and neurological evaluation at 6 and 24 months) in hypotensive infants	Original group was 191 infants, unclear how enrolled
D'Souza *et al.* (1995)[24]	$N=34$ (24–33 weeks)	Y	Not defined	Cohort Study	No effect of daily median BP on IVH	Small sample size
Perlman *et al.* (1996)[25]	$N=632$ (<1750 g)	N	Single mean BP on admission <25 mm Hg	Case control	Higher incidence of severe IVH if BP <25 mm Hg	Single BP threshold for all infants
Murphy *et al.* (1997)[26]	$N=59$ cases and 234 matched controls (<32 weeks)	N	Mean BP less than 30 mm Hg on two separate occasions	Case control study	Hypotension identified as a risk factor for IVH	Single BP threshold for all infants
Cunningham *et al.* (1999)[27]	$N=$ 232 (<1500 g)	N	BAPM rule	Cohort study. Excluded all those who died within 24 h	#1. No association between duration of BP <gestational age and IVH. #2. Increased IVH with lower BP the previous day	Actual BPs not given for result #2.
Meek *et al.* (1999)[28]	$N=24$ (24–31 weeks)	Y	Not defined	Selected infants with cerebral blood flow measurements	No association between lower BP and IVH	Small sample size, single BP measurement given for each patient

The four studies that appeared to satisfy the largest proportion of our criteria are described below in more detail. They each had repeated measurements of BP and reliable descriptions of cranial ultrasound findings.

Miall-Allen et al *[1987]* was the only study to use masked evaluation of the head ultrasound findings, they also had continuous invasive BP monitoring. They found an excess of IVH/PVL in hypotensive preterm infants, however the threshold
value was a single value of a mean BP less than 30mm Hg, and the sample size was only 33 infants of 26 to 0 weeks gestation, 9 of whom developed either a major IVH or PVL.

Bada et al. *[Perry EH, Bada HS et al 1990]* found that infants in whom grade 2 to 4 IVH developed had lower BP values for their post-natal age than matched control infants without IVH. However, the normal values were only derived from 16 infants less than 1 kg and it was not possible to calculate birth weight or gestation-specific BP thresholds from the presented data.

Watkins *[et al 1989]* reported a retrospective study which appears to have
included the entire cohort of VLBW admitted to the NICU. Having taken post-natal age and birth weight into account, they identified an association between prolonged duration of a BP below the 10th percentile for birth weight and post-natal age, and the frequency of IVH. However, there was no correction for other risk factors.

Cunningham *[et al 1999]* in a retrospective cohort study, reported that IVH
was associated with a 'low BP' the day before IVH, but no details are given regarding the schedules of echoencephalography or what was meant by low BP for this result. Furthermore, any infant with a mean arterial BP less than the gestational age in weeks received intervention with a colloid bolus followed by inotrope infusion, and other infants with BP above this threshold were treated if perfusion was poor. They excluded periods when infants received >10 ml/kg of colloid, which occurred in 83% of the infants under 750 g. They found no association between the development of IVH and the
duration of time when the mean BP was less than gestational age. All of these previous studies were confounded by the fact that pressor agents were used in at least some of the hypotensive infants.
Data from the Canadian Neonatal Network *[Barrington K et al 2002]* found a slightly increased risk of IVH in patients less than 28 weeks gestation whose
lowest recorded BP on day 1 was below their gestational age in weeks, and also when the lowest recorded BP was below the normal values produced by Watkins et al.[1989], but the associations disappeared after correcting for the use of pressor agents.
Martens et al. *[2003]* examined the influence of hypotension on abnormalities at term using the Prechtl examination, and defined hypotension as a mean BP<30mm Hg on at least two occasions. They found an association between hypotension defined in this way and an abnormal examination.
The study of the effects of hypotension on long-term outcomes by Goldstein et al. *[1995]* included infants less than 1500 g and defined hypotension as a systolic BP less than 35mm Hg for infants with a birth weight <750 g and <40mm Hg for 750 to 1500 g, regardless of post-natal age. They included BP measured both by cuff and indwelling arterial lines. They found a correlation between the duration of BP less than this threshold and lower psychomotor developmental index on the Bayley scales of infant development at 2 years.

Conclusions

This critical and systematic review reveals that there is very litte evidence to support the commonest current approaches to the management of hypotension in the newborn. There is insufficient evidence to define an acceptable BP. There is no evidence to suggest that intervention is associated with any improved long-term outcome; indeed it is possible that the contrary may be true; intervention is statistically associated with adverse outcomes *[Barrington K et al 2002, Heuchan AM et al 2002, Synnes AR et al 2001]*.
It is clear that some babies have poor peripheral oxygen delivery, and may require, and hopefully benefit from, intervention. These babies cannot, from this systematic review, be defined by any particular BP threshold. How best to diagnose these shock states and intervene will require further study. Physiologic studies of infants with shunts should measure systemic perfusion (right ventricular output or SVC flow) and

not just left ventricular output.
This lack of supportive information regarding the use of therapies to increase BP, all of which are potentially toxic *[de Zegher F et al 1993, Van den Berghe G et al 1996]*, is a major concern *[Evans JR et al 2006]*. In some NICUs, as many as 98% of the extremely low gestational age babies are exposed to these therapies *[Laughon M et al 2007]*. The entire paradigm of treating babies solely on the basis of a low mean arterial pressure should be revisited.
A combination of low BP with clinical signs of poor perfusion appears to be more strongly correlated with poor outcomes *[Dempsey EM 2005]* **A low systemic blood flow is also strongly associated with poor clinical outcomes, in particular the late occurrence (between 12 and 48 h of age) of a PVL/IVH** *[Kluckow M et al 2000]* **and of poor long-term neurodevelopment** *[Evans N 2006]*. Treating infants with either of these two criteria, which probably overlap, must be prospectively examined to determine whether outcomes are improved.

Abstract We aimed to assess the relationship between the clinical and biochemical parameters of perfusion and superior vena cava (SVC) flow in a **prospective observational cohort study of very low birth weight (VLBW) infants**. Newborns with congenital heart disease were excluded. Echocardiographic evaluation of SVC flow was performed in the first 24 h of life. **Capillary refill time (forehead, sternum and toe), mean blood ressure, urine output and serum lactate concentration were also measured simultaneously.** Thirty-eight VLBWinfants were examined. Eight patients (21%) had SVC flow less than 40 ml/kg/min. There was a poor correlation between the capillary refill time (in all sites), mean blood pressure, urine output and SVC flow. The correlation coefficient for the serum lactate concentration was r=−0.28, p=0.15. The median serum lactate concentration was 3.5 (range 2.8–8.5) vs. 2.7 (range 1.2–6.9) mmol/l (p=0.01) in low flow versus normal flow states. A serum lactate concentration of >2.8 was 100% sensitive and 60% specific for detecting a low flow state. Combining a capillary refill time of >4 s with a serum lactate concentration of >4 mmol/l had a specificity of 97% for detecting a low SVC flow state. Serum lactate concentrations are higher in low SVC flow states. **A capillary refill time of >4 s combined with serum lactate concentrations >4 mmol/l increased the specificity and positive and negative predictive values of detecting a low SVC flow state.**

Functional echocardiography may have a role to play inassessing the adequacy of circulatory status, as it can provide an objective evaluation of cardiac function, output, allow the identification of a significant patent ductus arteriosus and allow the evaluation of therapeutic interventions *[Kluckow M et al 2007]*.

Clinical evaluation is readily available to all, and a number of clinical and biochemical parameters are readily available at the bedside. These include the assessment of colour, capillary refill time, urine output, heart rate, actual base deficit and temporal change in acidosis and lactate values. Many of these parameters are subjective and their reproducibility is questionable. However, their inclusion with blood pressure values is likely to provide better information on the status of perfusion than reliance on absolute blood pressure values alone. This is important considering that there is no absolute blood pressure value threshold below which intervention results in improved outcome, nor is there a positive predictive value (PPV) for adverse outcome if the blood pressure falls below a particular value *[Dempsey EM et al 2007]*.

The superior vena cava (SVC) flow assesses blood flow from the upper body, and may provide a reliable assessment of systemic blood flow *[Kluckow M et al 2000]*. It is particularly useful on day 1 of life, as other measurements of cardiac output (left ventricular output, right ventricular output) are influenced by shunts across ductus arteriosus and atrial septum *[Evans N et al 1994, Evans N et al 1994]*. Low SVC blood flow has been associated with averse short-term and long-term outcome *[Hunt RW et al 2004, Kluckow M et al 2000, Osborne DA et al 2004, Osborne DA et al 2007]*.

Bedside detection of low systemic flow in the very low birth weight infant on day 1 of life

Miletin J. & Pichova K.& Dempsey E.M.

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Table 1 Clinical characteristics

	Low SVC, n=8	Normal SVC, n=30	Two-sided p-value
BW (median, kg) (range)	1.14 (0.56–1.44)	1.17 (0.57–1.48)	0.76
Apgar score, 1 min (median) (range)	5 (1–8)	6 (1–9)	0.23
Apgar score, 5 min (median) (range)	7 (4–9)	9 (3–10)	0.15
Gestational age (median, weeks) (range)	26.5 (24–29)	28.0 (24–31)	0.12
Gender (female %)	75	67	0.99
Surfactant (%)	100	63	0.08
Ventilation (%)	75	37	0.11
Mean airway pressure (median, cm H_2O) (range)	7.6 (0–10)	5.1 (0–8.1)	0.026
Patent ductus arteriosus (%)	100	83	0.56
Capillary refill time forehead (median, s) (range)	2.3 (1.5–4.3)	2.6 (1–4.7)	0.79
Capillary refill time sternum (median, s) (range)	2.9 (2.1–4.2)	2.8 (1.1–5.8)	0.56
Capillary refill time toe (median, s) (range)	3.5 (1.3–6.8)	3.1 (1.2–5.6)	0.63
Lactate (median, mmol/l) (range)	3.5 (2.8–8.5)	2.7 (1.2–6.9)	0.015
Urine output (median, ml/kg/h) (range)	2.6 (0.5–4.7)	3.1 (0–6.1)	0.50
Mean blood pressure (median, mm Hg) (range)	33 (15–49)	40 (24–62)	0.1

We have shown that mean blood pressure values are a poor marker of a low flow state and that the combination of readily available clinical and biochemical parameters may better determine low flow states.

CLINICAL QUESTION In newborn infants (patient) is capillary refill time test (CRT) an accurate marker of organ blood (flow outcome)?

SEARCH STRATEGY

Secondary sources

Review of Turning Research into Practice database and BestBETS revealed an evidence- based synopsis assessing the validity of CRT in paediatric intensive care, but no similar review for neonatal practice.

Primary sources

PubMed search with search terms (capillary refill time or capillary refilling time) and neonate revealed 31 papers.

On further review of abstracts 23 were excluded (2 review articles, 2 case reports, 8 not assessing CRT, 9 assessing CRT in non-neonatal age group, 2 comparing CRT with mortality) and 1 was unfortunately unavailable. The remaining seven studies are summarised below.

COMMENTS

Studies *[Strozik KS et al 1997, Strozik KS et al 1998, Raju et al 1999, LeFlore et al 2005]* measured CRT to determine normal values. Strozik *et al [Strozik KS et al 1997, Strozik KS et al 1998]* demonstrated a normal distribution of values when assessing central CRT, with values in normal infants below 3 sec. Using a similar method to assess CRT, however, LeFlore *et al [2005]* found longer CRT values with a wider normal range. This study is limited by its smaller sample size than *[Strozik KS et al 1997, Strozik KS et al 1998]* and because a single observer made all CRT measurements. These studies suggest that central CRT in normal, healthy neonates has a range of up to 4 s.

Raju *et al [1999]* attempted to define normal values for peripheral CRT in healthy newborns. The wide variation they found in healthy newborns (up to 10 s), fits with the widely scattered peripheral CRT values obtained by Strozik *et al*, and suggest that measuring peripheral CRT is of limited usefulness.

QUESTION 2
IS CAPILLARY REFILL TIME A USEFUL MARKER OF HAEMODYNAMIC STATUS IN NEONATES?

Gale C.

Arch Dis Child **2010**;95:395–397.doi:10.1136/adc.2010.186411

No studies assessing normal CRT values *[Strozik KS et al 1997, Strozik KS et al 1998, Raju et al 1999, LeFlore et al 2005]* followed up the samples in the short term to ensure there were no conditions (such as congenital heart disease) that might have affected the CRT values obtained; however, these conditions are sufficiently rare in infants with normal observations, and the samples are large enough, that these studies should still give
a good determination of normal values.
Studies *[Wodey E et al 1998, Osborne DA et al 2004, Evans N 1996]* compare CRT with echocardiographic measures of systemic blood flow. Use of ventricular output measures (such as cardiac index) is complicated by the presence of shunts across the developing heart (foramen ovale and ductus arteriosus). As a result, these ventricular measures can significantly overestimate systemic blood flow *Evans N 1996]*. Wodey *et al*'s paper *[Wodey E et al 1998*] used cardiac index as the gold standard marker of systemic blood flow with which to compare peripheral CRT. The questionable validity of the gold standard as a measure of systemic blood flow, and the use of peripheral CRT as comparison, limits the validity of their findings.
To overcome this problem flow can be measured at the superior vena cava (SVC), representing blood flow returning from (and thus flowing to) the head and upper body. SVC flow has been validated as a gold standard *[Hunt RW et al 2004, Osborne DA 2003]*. Osborn *et al [2004]* compared central CRT to SVC flow over the first day of life. Inotropes were commenced following detection of low SVC flow on echocardiography (6% commenced on inotropes at 5–10 h, 33% at 24 h). Commonly used inotropes have an effect on peripheral vascular tone and therefore on CRT (epinephrine, a powerful peripheral vasoconstrictor prolonging CRT, and dobutamine, which has peripheral vasodilator actions leading to decreased CRT). Only 12% of values were recorded following inotrope administration, so a robust correlation between CRT and SVC flow should still be apparent.
These findings support the use of CRT in assessing low SVC flow and provide useful LRs. Miletin *et al [Miletin J 2009]* performed a very similar, smaller study, which did not replicate the findings of Osborn *et al*. However, over half of the group with low SVC flow detected on echocardiography had already been started on inotropic support at the time of assessment, compared with 3% of the normal SVC flow group. The agents used would be expected to have significant effects on CRT, and in combination with the small sample size the importance of these results is limited.

Clinical bottom line

(1) Central capillary refill time (CRT) seems to have a wide range of normal values (up to 4 s) in newborn infants (grade B).
(2) Peripheral CRT is not a useful assessment of haemodynamic status in neonates (grade B).
(3) Central CRT values ≥4 s may represent significantly reduced organ blood flow (likelihood ratio 7.25 in <30-week gestation infants) (grade B).

Table 1 Is capillary refill time a useful marker of haemodynamic status in neonates?

Citation	Study group	Study type (level of evidence)	Outcome	Key result (mean (SD 95th centile))	Comments
Strozik *et al*[1]	469 Healthy neonates, 28–42 weeks' gestation, single unit, normal observations for preceding 24 h. CRT—5-s pressure, in sternum, forehead, hand and heel	2b, Prospective cohort study with poor follow-up	CRT: Head Chest Hand Foot	*Mean (SD, 95th centile)* 1.73 s (0.37 s, 2.26 s) 1.9 s (0.38, 2.65 s) Non-normal distribution. Non-normal distribution	Ambient temperature controlled. No significant interobserver variability. No long-term follow-up (to ensure healthy sample)
Strozik *et al*[2]	280 Healthy term newborns, single unit, normal observations for preceding 24 h. CRT measured on day 2 or 3. CRT—hand, head and chest Divided into seven groups, with seven different CRT pressure times (1–7 s)	2b, Prospective cohort study with poor follow-up	CRT: Head (3 s) Head (7 s) Chest (3 s) Chest (7 s) Hand	*Mean (SD, 95th centile)* 1.76 s (0.31 s, 2.37 s) 1.88 s (0.39 s, 2.52 s) 1.76 s (0.32 s, 2.39 s) 1.82 s (0.35 s, 2.51 s) No significant difference between 3 and 7 s pressure times Non-normal, widely scattered distribution	Different patient set from paper.[1] No significant interobserver variability. No long-term follow-up of sample
Raju *et al*[3]	137 Normal newborn term infants, single unit (45, <24 h; 47, 24–48 h; 45, 48–72 h). CRT—5 s pressure, in hand and foot. Triplicate measurements. Ambient and skin temperature measured	2b, Prospective cohort study with poor follow-up	Triplicate measurement. Temperature. CRT: Hand Foot	*Mean (SD, 95th centile)* 4.23 s (1.47 s, 7.11 s) 4.64 s (1.41 s, 7.4 s) Decreasing CRT with each subsequent assessment Inverse relation between CRT and temperature	No long-term follow-up of sample. Only peripheral CRT measured
LeFlore *et al*[4]	42 Healthy, term infants, single unit. CRT measured 1–4 h after birth, compared with non-invasive BP and heart rate (gold standards). CRT—finger, heel, chest. Pressure 1–2 s (brief) and 3–4 s (extended)	4, Poor reference standard	CRT. Brief pressure (chest). Extended pressure (chest)	*Mean (SD, 95th centile)* 2.4 s (0.6 s, 3.58 s) 3.8 s (0.8 s, 5.37 s) No significant correlation with heart rate and CRT. Direct relation with BP and CRT	No long-term follow-up of sample. Non-relevant gold standards (BP and heart rate) in healthy infants. No mention of blinding
Wodey *et al*[5]	100 Infants, single unit CRT compared to cardiac index as gold standard CRT—average of hands and feet, 5 s pressure	4, Poor reference standard	Peripheral CRT	Significantly correlated with cardiac index	No definition of abnormal cardiac index (as gold standard). No reference for validity of gold standard. No clear mention of CRT values
Osborn *et al*[6]	128 Infants, <30 weeks' gestation, two units CRT, invasive BP and CPTd measured and compared to SVC flow (gold standard), at 3 h, 5–10 h and 24 h' CRT—5 s pressure, chest and hand	2b, Exploratory cohort study with good reference standard	Chest CRT. Chest CRT	Correlation between chest CRT and low SVC flow. Area under ROC 0.72 (95% CI 0.64 to 0.80). ≤3 s: LR for low SVC flow 2.75. ≤4 s: LR for low SVC flow 7.25	Gold standard validated.[7 8] Appropriate spectrum of patients. Gold standard applied regardless of CRT result. No mention of blinding
Miletin *et al*[9]	38 VLBW infants, single unit. CRT, BP, serum lactate and UO measured and compared to SVC flow (gold standard), in first 24 h (median 18 h). CRT measured at head, chest and foot. Pressure applied for 5 s	2b, Exploratory cohort study with good reference standard	CRT (chest, head), UO, BP. Lactate, CRT (foot)	Poor positive correlation with SVC flow. Poor negative correlation with SVC flow	Gold standard same as[6] CRT measured by staff blinded to other parameters. 50% Of low SVC flow group on inotropes at time of assessment

BP, blood pressure; CPTd, core periphery temperature difference; CRT, capillary refill time, LR, likelihood ratio; ROC, receiver operating characteristic curve; SVC, superior vena cava, UO, urine output; VLBW, very low birth weight (<1500 g).

Kokkuvõtte (abstract või kokkuvõtlikum info)	**Viide kirjandusallikale**
ABSTRACT **Purpose:** Hypotension is a frequent occurrence in sick preterm neonates. It is important to appropriately recognise and treat hypotension in preterm infants due to the possible association with short and long term adverse outcomes. **Search Strategy:** An extensive search for relevant articles was carried out on PubMed, Embase and Cochrane database of systematic reviews. Cross	**Hypotension in Preterm Infants** **IBRAHIM H** INDIAN PEDIATRICS **2008** VOLUME 45,

references were hand searched.

DEFINITION OF HYPOTENSION IN PRETERM NEONATES

Blood pressure in preterm infants can be measured both invasively, using intra-arterial catheters and non-invasively. Invasive blood pressure measurement is the gold standard *[Weindling AM 1989, Nuntnarumit P et al 1999]*. In hypotensive newborns non-invasive measurements tend to overestimate blood pressure *[Diprose GK et al 1986]*. Invasive pressure monitoring has it's problems too.

The pressure reading is affected by the mechanical properties of the intra-arterial catheter and the transducer system and presence of air bubbles. The above factors cause excessive damping leading to low systolic and high diastolic readings *[Weindling AM 1989, Nuntnarumit P et al 1999]*.

Mean blood pressure is less affected by these and hence reliable even in the presence of a damped trace [*Nuntnarumit P et al 1999]*.

'Normal' blood pressure should be defined as the pressure, which ensures adequate organ perfusion *[Subhedar NV 2003, Dasgupta SJ et al 2003]*. The normal values will depend on gestational age, birthweight and postnatal age. Many studies have attempted to establish normal blood pressure ranges for very low birth weight (VLBW) infants.

Cunningham, et al[1999] have analyzed computerized data on a large cohort of patients over a 5-year period. After removing artifacts, excluding children with IVH and those on inotropic support they have published normative data for the first seven days of life in VLBW infants. They defined hypotension as less than the 10th centile for birth weight and postnatal age. This is a comprehensive dataset and probably serves as a useful reference range:

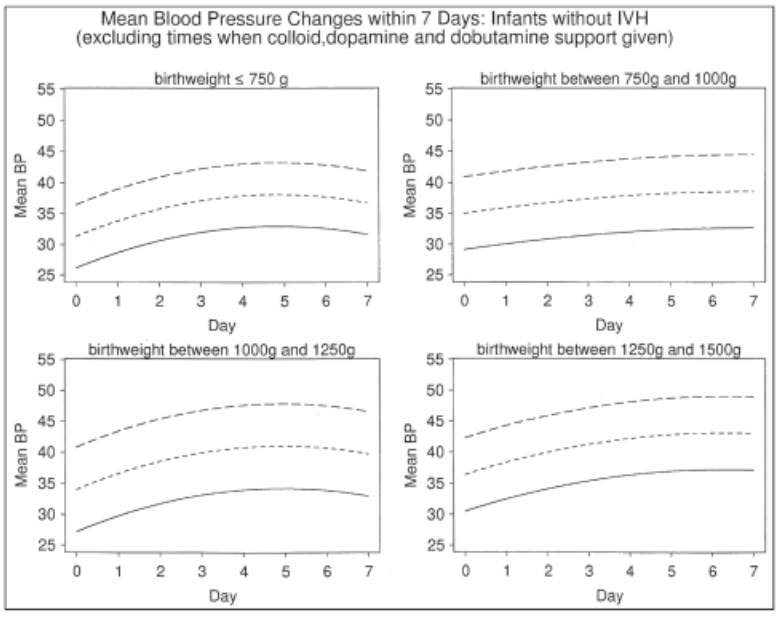

FIG. 1. Normal blood pressure ranges for very low birth weight infants in the first 7 days of life.

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They also examined the recommendations made by some authors that a blood pressure above 30mm of Hg should be maintained to prevent cerebral injury *[Miall-Allen VM et al 1987, Bada HS 1990]*. The authors found no difference in cerebral perfusion between groups with mean arterial blood pressure above or below 30 mm of Hg. But the minimum blood pressure required to maintain cerebral perfusion is unclear and the current treatment thresholds for hypotension suggested by various authors based on 'normal' blood pressure ranges are at best arbitrary. There is also evidence emerging that cardiac output rather than mean arterial blood pressure is a more important determinant of cerebral oxygen delivery *[Kissack CM et al 2004]*.

HYPOTENSION AND CEREBRAL INJURY

Periventricular hemorrhage: Periventricular hemorrhage is an important cause of long-term morbidity in preterm infants *[de Vires LS et al 1999]*. Many studies have shown an association between low systemic blood pressure and intra-ventricular hemorrhage *[Watkins AM et al 1989, Cunningham S et al 1999, Miall-Allen VM et al 1987, Bada HS 1990]*. Miall-Allen, et al. demonstrated a significant relationship between a mean blood pressure of less than 30 mm of mercury and significant cerebral lesions in very low birthweight infants *[Miall Allen et al. 1987]*.

Periventricular leukomalacia: Miall Allen, et al. *[1987]* found a higher incidence of severe abnormalities including cystic PVL in preterm neonates who had a mean blood pressure less than 30 mm Hg.

PATHOPHYSIOLOGY OF HYPOTENSION IN PRETERM INFANTS

Blood pressure is dependent on cardiac output and systemic vascular resistance. Cardiac output is determined by preload, myocardial contractility and afterload *[Engle WD 2001]*. The contribution of left ventricular output towards maintenance of blood pressure in very low birthweight infants is unclear. More than one researcher has found a normal or high ventricular output in hypotensive preterm infants *[Pladys P et al 1999, Lopez SL et al 1997]*.

These babies often have a low systemic vascular resistance, often associated with a significant shunt across a PDA. Kluckow, et al. *[1996]* found a weak correlation between left ventricular output and blood pressure in preterm infants after accounting for ductal shunting. Myocardial dysfunction may be a factor in preterm hypotension. Gill and Weindling in a study on 75 low birth weight infants found a myocardial dysfunction in approximately half of the hypotensive infants *[Gill AB et al 1993]*. But other studies have failed to show such an association *[Pladys P et al 1999, Lopez SL et al 1997]*. Low circulating volume does not seem to be a major contributor towards preterm hypotension.

MANAGEMENT OF HYPOTENSION

The treatment of neonatal hypotension should be based on an overall assessment of cardiovascular status of the infant and not blood pressure alone. The heart rate, peripheral perfusion and urine output should be considered in addition to blood pressure *[Subhedar NV 2003]*. An elevated lactate concentration on blood gas analysis

indicates low tissue perfusion in the absence of metabolic diseases. The value of CVP monitoring in preterm new-borns with systemic hypotension is uncertain, but serial measurements may guide use of volume expansion *[Subhedar NV 2003, Skinner JR et al 1992]*. Echocardiographic evaluation can serve as useful adjunct, but is not readily available in most neonatal units. But many studies strongly indicate that absolute hypovolemia is an infrequent cause of hypotension in the preterm infant *[Seri I et al 2001]*. Bauer, et al.*[1993]* in study on 43 preterm infants did not find a correlation between systolic blood pressure at normal blood volumes. Lundstrom, et al.*[Lundstrom K et al 2000] f*ound that volume expansion increased cardiac output without any effect on blood pressure in preterm infants. **KEY MESSAGES** **• Majority of hypotensive preterm infants are not hypovolemic and hence overzealous fluid administration is to be avoided.** **• Dopamine is the first line inotrope of choice.** **• Steroids can be used in inotrope resistant hypotension** **SUMMARY AND CONCLUSIONS** The importance of hypotension lies in the presumed effect of blood pressure variations on cerebral blood flow apart from other organ perfusion. Though majority of the hypotensive infants are not hypovolemic, a fluid bolus could potentially improve cardiac output. Infants who are hypotensive despite volume expansion require inotropic support. Dopamine seems more effective than dobutamine in improving blood pressure. Experience with other inotropes is limited. Steroids may be used in hypotension refractory to high doses of ionotropes. Other physiological parameters need to be optimised along with pharmacological and fluid management of hypotension.	
Background: Extremely preterm babies (delivered at <28 completed weeks of gestation) are frequently diagnosed with hypotension and treated with inotropic and pressor drugs in the immediate postnatal period. Dopamine is the most commonly used first-line drug. Babies who are teated for hypotension more frequently sustain brain injury, have long-term disability or die compared to those who are not. Despite the widespread use of drugs to treat hypotension in such infants, evidence for efficacy is lacking, and the effect of these agents on long-term outcomes is unknown. **Current Practice, Clinical Uncertainty** While hypotension is statistically associated with adverse short- and long-term outcomes, a systematic review of the literatuure was unable to find clear criteria to define hypotension *[Dempsey EM et al 2009]*. There is no consensus on threshold definitions for hypotension in preterm infants. Many clinicians rely on absolute mean BP values alone to guide intervention. BP reference ranges are often based on birth weight, gestational age (GA) and postnatal age criteria *[Lee J et al 1999, Spinazzola RM et al 1991, Watkins AM et al 1989, Versmold HT et al 1981, Hegyi T et al 1994, Hegyi T et al 1996]*. These statistically determined values vary considerably as they are based on	**Management of Hypotension in Preterm Infants (The HIP Trial): A Randomised Controlled Trial of Hypotension Management in Extremely Low Gestational Age Newborns** Dempsey E.M., Barrington K.J. N. Marlow N., O'Donnell C.P., Miletin J., Naulaers G., Cheung P.-Y., Corcoran D., Pons G., Stranak Z., Laere

observations of BP made in small cohorts of infants, the majority of whom were born before the widespread implementation of important perinatal interventions (e.g. antenatal glucocorticoid therapy) which are known to improve outcome and reduce the incidence of intraventricular haemorrhage in preterm infants *[Bada H et al 1990]*. The Joint Working Group of the British Association of Perinatal Medicine has recommended that the mean arterial BP (mm Hg) **should be maintained above the GA (weeks) (e.g. an infant born at 25 weeks of gestation should have a mean BP >25 mm Hg)** *[Development of audit measures and guidelines for good practice in the management of the neonatal respiratory distress syndrome 1992]* . **Despite litte published evidence to support this 'rule', it remains the most commonly used criterion to define intervention and it has been used in a number of recent randomised therapeutic intervention trials where it was the sole entry criterion** *[Pellicer A et al 2005]* . It is uncertain whether hypotension (however defined) results in adverse clinical outcomes, including adverse short-term outcomes (increased incidence of intraventricular haemorrhage) *[Miall-Allen VM et al 1987]* and adverse long-term neurodevelopmental outcomes *[Martens et al 2003, Murphy D et al 1995, O`Shea T 1997]*. Furthermore, it is unclear whether intervention to treat hypotension results in improved outcomes. Dopamine, the most commonly used agent, has not been shown to improve clinical outcomes. **Evaluating Systemic Perfusion** Currently, there is no validated clinical scoring system to diagnose shock – or failure of systemic perfusion – in preterm infants, and assessment of the adequacy of endorgan blood flow is mostly subjective. **Clinical evaluation includes assessment of capillary refill time, skin colour, temperature and urine output. Capillary refill time values exist for term newborns** *[Raju NV et al 1999***], but there are limited data available for preterm infants** *[Wodey E et al 1998, Osborne DA et al 2004]***. Although there is a significant relationship between cardiac index (cardiac output/body surface area) and capillary refill time in preterm babies, there appears to be only a weak association between capillary refill and systemic blood flow *[Wodey E et al 1998]* .** We previously identified a weak relationship between capillary refill values and simultaneously obtained echocardiographic **measures of superior vena cava (SVC) flow** *[Miletin J et al 2009]*. Though the glomerular filtration rate rises rapidly after birth, urine output is low and variable in the first 24 h, the period when preterm infants are most commonly treated for hypotension, making it a less useful measurement. Indeed, none of these parameters in isolation is specific for identifying poor perfusion. **Whilst the positiive predictive value of each of these individual measures for identifying poor perfusion is low, it appears that using a combination of signs may allow identification of patients at higher risk of poor outcomes** *[Dempsey EM et al 2009]* **. Biochemical methods used to evaluate the adequacy of end-organ perfusion include the measurement of seerum levels of lactate, an**	D.V. on behalf of the HIP Consortium Neonatology, **2014**; 105:275–281 DOI:.1159/000357553

acid produced during anaerobic metabolism.
Lactate values have been analysed in a number of clinical situations in the preterm infant, including the need for erythrocyte transfusion, sepsis *[Fitzgerald MJ et al 1992]* and necrotising enterocolitis *[Abubacker M et al 2003]*. **Elevated or increasing values obtained on the first day of postnatal life are associated with increased mortality in preterm and term newborns *[Groenendaal F et al 2003, Deshpande SA et al 1997].* A single lactate value >5.6 mmol/l obtained on the first day was associated with an increased risk of averse outcome, defined as death or severe intraventricular haemorrhage** *[Nandeem M et al 2010]* . In contrast, Wardle *[1999]* found no difference in lactate levels between normotensive and hypotensive preterm infants. We identified a weak negative correlation between lactate values and SVC flow in a cohort of very low birth weight infants. Combined lactate values of >4 mmol/l and prolonged capillary refill times >4 s resulted in a positive predictive value of 80% and a negative predictive value of 88% for identifying low SVC flow, highlighting the value of combining clinical and biochemical parameters *[Miletin J et al 2008*] in the assessment of the adequacy of end-organ blood flow.
Current standard approaches to the evaluation and treatment of transitional circulatory problems in the preterm infant are not evidence based. We recently established the HIP (Hypotension in Preterm Infants) Consortium, comprising neonatologists, scientists, pharmacologists and industry partners. The Seventh Framework of the European Union funds the consortium. HIP is designed to evaluate two strategies in a randomised controlled trial, and define the efficacy of the most commonly used inotropic medication, dopamine (EudraCT No. 2010-023988-17; Clinical Trial Registration No.: clinical trials.gov NCT01482559).
A combination of BP values and clinical signs/biochemical findings will be used to determine whether an infant should subsequently receive rescue treatment.
There are two criteria for rescue treatment, either a mean BP value >5 mm Hg below threshold or a combination of two or more signs reflecting poor perfusion, namely a mean BP value 3 mm Hg below threshold, lactate >4 mmol/l or a capillary refill time >4 s.
Hypothesis:
In extremely preterm babies, restricting the use of dopamine when mean blood pressure (BP) values fall below a nominal threshold and using clinical criteria to determine escalation of support ('restricted' approach) will result in improved neonatal and longer-term developmental outcomes.
Research Plan: In an international multi-centre randomised trial, 830 infants born at <28 weeks of gestation, and within 72 h of birth, will be allocated to 1 of 2 alternative treatment options (dopamine vs. restricted approach) to determine the better strategy for the management of BP, using a conventional threshold to commence treatment. The first co-primary outcome of survival without brain injury will be determined at 36 weeks' postmenstrual age and the

second coprimary outcome (survival without neurodevelopmental disability) will be assessed at 2 years of age, corrected for prematurity.

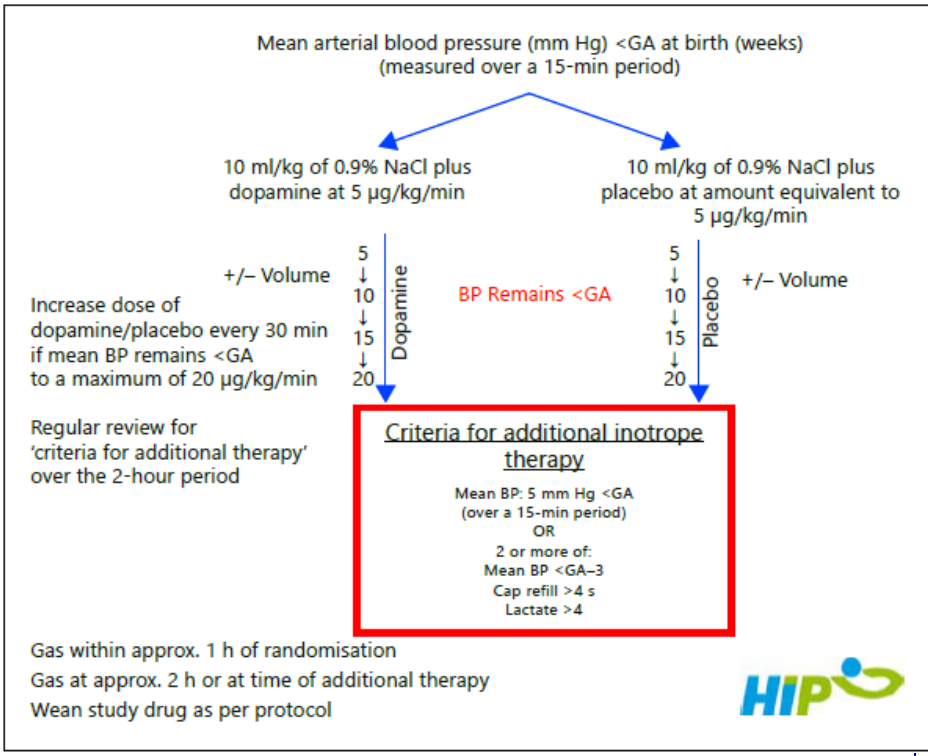

Fig. 1. Treatment algorithm for the management of low BP in extremely preterm infants during the first 72 h of life.

Discussion: It is essential that appropriately Designer trials be performed to define the most appropriate management strategies for managing low BP in extremely preterm babies.

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Search **((((((((((((((((("premature infant") OR "premature infants") OR "premature newborn") OR "premature newborns") OR "premature neonate") OR "premature neonates") OR "preterm infant") OR "preterm infants") OR "preterm newborn") OR "preterm newborns") OR "preterm neonate") OR "preterm neonates")) OR (("Infant, Premature"[Mesh]) OR "Infant, Low Birth Weight"[Mesh])))) AND ((hemodynamic assessment) OR "Hemodynamics"[Mesh])) AND ((systematic[sb] OR Randomized Controlled Trial[ptyp] OR Guideline[ptyp] OR Controlled Clinical Trial[ptyp]) AND "last 10 years"[PDat])))) AND (((((criterions) OR criteria) OR criterion) OR measure) AND ((systematic[sb] OR Randomized Controlled Trial[ptyp] OR Guideline[ptyp] OR Controlled Clinical Trial[ptyp]) AND "last 10 years"[PDat]))**