Kliiniline küsimusnr 27

1. Kas kõikidel infektsiooni riskiteguritega enneaegsetel vastsündinutel kasutada ravitulemi parandamiseks profülaktilist antibakteriaalset ravi võrreldes mitte kasutamisega?
   - penitsilliin+gentamütsiin võrreldes ampitsilliin+gentamütsiin
   - kestus/lõpetamise näidustused– kas/millal on ohutu lõpetada negatiivsete külvide korralja põletikunäitajate puudumisel
   - antibakteriaalse ravi kestus koorionamnioniidiga rasedusest sündinud enneaegsel

Kriitilised tulemusnäitajad:lapse peamised tulemusnäitajad

Ravijuhendid

Kokkuvõte ravijuhenditest

1. Antibiotics for early-onset neonatal infection: antibiotics for the prevention and treatment of early-onset neonatal infection

National Collaborating Centre for Women's and Children's Health Commissioned by the National Institute for Health and Clinical Excellence - **(NICE) August 2012.** Published by the Royal College of Obstetricians and Gynaecologists (RCOG). **Evidence Update June 2014.**

NICE kliinilises ravijuhendis esitatud soovitused käsitlevad antibakteriaalset ravi vastsündinu varase algusega infektsiooni (kuni 72 tundi peale sündi) preventsiooniks ja raviks, mis on avaldatud 2012. aastal (tõendid kuni 22.09.11.) ja täiendatud 2014. aastal (lisatud uued tõendid ajavahemikust 01.09.11.-15.01.14.) Ravijuhendis käsitletud uuringutesse olid kaasatud enneaegsed ja ajalised vastsündinud. Ravijuhend on kõrge kvaliteediga.

NICE ravijuhendi soovitused 2012, 2014

Infektsiooni riskitegurid ja infektsiooni võimalikud kliinilised näitajad

-Kui vastsündinul on mõni "suur riskitegur" või 2 või rohkem "riskitegurit" või kliinilist sümptomit (vt. Tabel 1 ja 2**), teosta uuringud ja alusta antibakteriaalse (AB) raviga.** Ära viivita AB raviga testide tulemuseni, alusta empiirilist intravenoosset antibakteriaalset ravi.

-Esmase AB valikuna kasuta: bensüülpenitsilliini koos gentamütsiiniga (kui kohalik mikrobioloogiline seire ei ole tuvastanud resistentsust ja vajalik on erineva antibiootikumi kasutamine)

Vajalikud uuringud riskiteguritega või kliiniliste sümptomitega vastsündinul:

-CRV; - verekülv enne I AB doosi.

-Lumbaalpunktsioon:teosta enne AB ravi alustamist, kui on tugev kliiniline kahtlus infektsioonile (sepsisele) või meningiidile viitavad kliinilised sümptomid.

-Kui laps vajab AB ravi, alusta alati niipea kui võimalik ja alati 1 tunni jooksul ravi alustamise otsusest

-Infektsiooniriskitegurite või võimaliku infektsiooni kliiniliste sümptomite tõttu alustatud AB ravi ajal määra kordus CRV 18-24 tundipärast antibiootikumidega ravi alustamist

-Kaalu lumbaalpunktsiooni tegemist, kui esialgu seda ei tehtud ja lapsel on:

CRV ≥10mg/l või on positiivne verekülv või on mitterahuldav vastus AB ravile või on tugev kliiniline kahtlus sepsisele/meningiidile.

-**Hinda regulaarselt uuesti lapse kliinilist seisundit ja uuringute tulemusi, AB võib vajada muutmist:** kui lapse kliiniline seisund ei parane, olemas mikrobioloogilise uuringu tulemused, ekspert mikrobiloogi soovitused arvestades kohalikke olusid. Kui mikrobioloogiliselt on tõendeid gramnegatiivsest bakteriaalsest sepsisest, lisa teine antibiootikum bensüülpenitsilliinile ja gentamütsiinile, mis on aktiivne gramnegatiivsetele bakteritele (näit. **tsefotaksiim**) -lõpeta bensüülpenitsilliin, kui on kinnitunud gramnegatiivne infektsioon.

-**Kui peale sündi vastsündinul ei ole kõrgeid riskitegureid ja on ainult 1 riskitegur või 1 kliiniline sümptom, kasuta kliinilist otsustamist** – kas on ohutu AB raviga mitte alustada ja kas on vajalik monitoorida lapse elulisi näitajaid ja kliinilist seisundit – kui monitooring on vajalik, jälgi last vähemalt 12 tundi (0, 1 ja 2 tunni vanuselt, edasi 2 tunni tagant 10 tunni jooksul)

Infektsiooni riskitegurid ja infektsiooni võimalikud kliinilised näitajad –>kasuta riskitegureid, kliinilisi näitajaid ja kõrgeid riskitegureid AB ravi alustamise otsustamiseks.

1. Vastsündinu varase algusega infektsiooni riskitegurid **EONI (early onset neonatal infection) - Tabel 1** **Riskitegur**	**Suur riskitegur**
Invasiivne B-grupi streptokokk infektsioon eelmisel lapsel	
Ema GBS kolonisatasioon, GBS bakteriuuria või infektsioon käesoleva raseduse käigus	
Lootevee puhkemine enne sünnitustegevust	
Spontaanse sünnitustegevuse järgselt enneaegne sünnitus (<37.nädalat)	
Kahtlus või kinnitunud lootevee puhkemine >18 tunni enneaegse sünnituse korral	
Sünnitusaegne palavik >38C või kinnitunud või kahtlus koorionamnioniidile	
Parenteraalne AB ravi emale kinnitunud või invasiivse bakteriaalse infektsiooni kahtlusel (septitseemia) sünnituse ajal või 24 tundi enne ja pärast sünnitust (see ei käi sünnitusaegse antibakteriaalse profülaktika kohta)	**jah**
Kahtlus või kinnitunud teise lapse infektsioon mitmikraseduse korral	**jah**
Tabel 2 **2. Kliinilised sümptomid võimaliku vastsündinu varase infektsiooni korral**	**Suur riskitegur**
Respiratoorne düstress algusega 4 tundi pärast sündi	**jah**

Krambid	**jah**
Mehhaanilise ventilatsiooni vajadus ajalisel lapsel	**jah**
Šoki sümptomatoloogia	**jah**
Muutunud lihastoonus (näit. hüpotoonia)	
Muutunud käitumine või reageerimisvõime	
Toitmisraskused (näit. toidust keeldumine)	
Toidutalumatus (k.a. oksendamine, suured maojäägid ja kõhu distensioon)	
Südamesageduse muutused - bradükardia, tahhükardia	
Hüpoksia (näit. tsentraalne tsüanoos või madalam hapniku saturatsioon)	
Ikterus 24 tunni jooksul peale sündi	
Apnoe	
Neonataalse entsefalopaatia tunnused	
Kardiopulmonaalse elustamise vajadus	
Mehhaanilise ventilatsiooni vajadus enneaegsel vastsündinul	
Persisteeruv lootevereringe (persisteeruv pulmonaalne hüpertensioon)	
Termolabiilsus (alla 36˚C või üle 38˚C, seletamatu keskkonna tingimustega)	
Ebaselge põhjusega suur verejooks, trombotsütopeenia või ebanormaalne koagulatsioon (international normalised ratio greater than 2,0)	
Oliguuria üle 24tunni peale sündi	
Häirunud glükoosi metabolism (hüpoglükeemia, hüperglükeemia)	
Metaboolne atsidoos (BE -10mmol/l või rohkem)	
Lokaalsed infektsioonikolded (näit. nahk või silmad)	

-**Väldi vastsündinul rutiinselt antibiootikumide kasutamist, kui ei esine riskitegureid infektsioonile või kliinilisi sümptomeid või laboratoorseid tõendeid võimalikust infektsioonist**.

-**EONI kahtluse korral**: uuringutest ei ole vaja rutiinselt teostada uriini mikroskoopiat või baktriaalsetkülvi; ei ole vaja nahalt võtta kaabet mikroskoopiaks või bakteriaalset külvi, kui puuduvad lokaalsed nahainfektsiooni tunnused.

-**Kerge konjunktiviit võib vastsündinul esineda, purulentse konjunktiviidi** korral võib esineda tõsine infektsioon (klamüüdia või gonokokkinfektsioon), võta mikrobioloogiline külv. Alusta süsteemset AB ravi võimaliku gonokokkinfektsiooni kahtlusel külvide vastuste saabumiseni.

-**Kliiniliselt nabainfektsiooni** esinemisel, purulentse eritise või periumbilikaalse tselluliidi tunnnuste korral (näit. punetus, tõusnud naha soojus või lõhn), võta verekülv, bakteriaalne külv, mikroskoopiaks kaabe ja alusta i/vAB ravi flukloksatsilliiniga ja gentamütsiiniga. Kui mikrobioloogia vastus ei näita gramnegatiivset infektsiooni, lõpeta ravi gentamütsiiniga.

Antibakteriaalse ravi kestus - otsused 36 tundi pärast AB ravi alustamist

-kui laps sai AB ravi infektsiooni riskitegurite või kliiniliste sümptomite tõttu – **kaalu AB ravi lõpetamist juhul kui: verekülv on negatiivne, esmane kliiniline kahtlus infektsioonile ei olnud tugev ja lapse kliiniline seisund on stabiilne, viideteta võimalikule infektsioonile ja CRV tase endiselt madal.**

-**Varase algusega infektsioon (meningiidita): positiivse verekülvi korral ja vastsündinutel, kellel verekülv on negatiivne, kuid on tõsine kahtlus sepsisele - AB ravi tavaliselt kestusega 7 päeva**. Kaalu ravi kestust üle 7 päeva, kui laps ei ole veel täielikult tervenenud või see on soovitav, baseerudes verekülvist identifitseeritud patogeenile (pöördu mikrobioloogilise konsultatsiooni suhtes eksperdi poole).

-**AB ravi jätkamisel üle 36 tunni vaatamata negatiivsetele verekülvidele,** vaata last vähemalt 1 kord 24 tunni jooksul. Iga kord kliinilisel otsustamisel kaalu, kas on on asjakohane AB ravi lõpetada: arvesta esialgset kliinilist kahtlust infektsioonile, lapse kliinilist progressi ja käesolevat seisundit, CRV taset ja suundumust.

-**Meningiidi kahtlusel, kui patogeen on veel teadmata, rakenda ravii/v amoksitsilliiniga ja tsefotaksiimiga**; kui on gramnegatiivne infektsioon (liikvoris või külvis), lõpeta amoksitsilliin, ravi ainult tsefotaksiimiga. Kui liikvoris on grampositiivne infektsioon, jätka ravi i/v amoksitsilliini ja tsefotaksiimiga, oodates liikvori külvi vastust.

Kui liikvori külv on positiivne GBS-le: muuda AB doosi.

-Kui verekülvis või liikvori külvis on *Listeria monocytogenes,* kaalu tsefotaksiimi lõpetamist ning ravi amoksitsilliini ja gentamütsiiniga.

Gentamütsiini terapeutiline monitooring

Enne II doosi gentamütsiini manustamist, kontrolli gentamütsiini madalaimat kontsentratsiooni veres, tee seda ka enne III doosi manustamist. Edaspidi mõõda enne igat III doosi ravimi kontsertatsiooni veres, vajadusel sagedamini.

Korrigeeri gentamütsiini doosi intervalli, eesmärgiga saavutada madalaim kontsentratsioon alla 2mg/l. Kui gentamütsiini kuur kestab üle 3doosi, madalaim kontsentratsioon on soovitav alla 1mg/l.

Kui kavatsetud kontsentratsiooni mõõtmist pole võimalik teha, siis tee järgmine doos ikkagi ära v.a. juhul, kui on tegemist renaalse düsfunktsiooniga (uurea või kreatiniini tõus või anuuria).

Kaalu gentamütsiini kõrgeimat kontsentratsiooni (peak concentration) mõõtmist selektiivselt: ödeem, makrosoomia,ravile ebapiisav vastus, tõendatud gramnegatiivne infektsioon. **Mõõda kontsentratsiooni 1 tund peale gentamütsiini infusiooni alustamist. Kui lapsel on gramnegatiivne või stafülokokk infektsioon, kaalu gentamütsiini doosi suurendamist, kui kõrgeim kontsentratsioon on alla 8mg/l.**

– Uuendatud NICE ravijuhenditõendid 2014

uued tõendid ei asendanud NICE juhendit ja ei toonud formaalseid praktilisi soovitusi, ei omanud potentsiaalset mõju juhisele

1. Riskitegurid infektsioonile, kliinilised näitajad infektsioonile – epiduraalanesteesia võib olla riskiteguriks varase vastsündinu palaviku tekkel, sõltumata sünnitusaegsest palavikust, aga ei ole seotud kõrgema neonataalse infektsiooni esinemissagedusega

2. Uuringud enne AB ravi alustamist vastsündinul: täisvere analüüs – varem kasutati leukotsüütide arvu, absoluutset neutrofiilide arvu ja ebaküpsete neutrofiilide ja küpsete

neutrofiilide üldarvu suhet (I:T) asümptomaatilistel vastsündinutel varase algusega infektsiooni diagnoosimiseks koos vähemalt ühe riskiteguriga. **Täisvere analüüs** - diagnostilise testi täpsus ei ole piisavalt tugev, et soovitada kasutamiseks vastsündinutel AB ravi alustamisel. **Täisvere analüüsi näitajad ei pruugi olla piisavalt sensitiivsed välistamaks varase algusega infektsiooni vastsündinul, juhised ei soovita EONI diagnoosimiseks.**

Seerumi prokaltsitoniin – kättesaadavate tõendite heterogeensus seerumi prokaltsitoniini kontsentratsiooni kasutamisest neonataalse sepsise diagnoosimisel takistab kindlaid järeldusi tegemast, **diagnostiliste väärtuste mõju ei olnud oluline.**

3. Antibiootikumid infektsiooni kahtluse korral: gentamütsiini doseering– laiendatud doosi reziim 5mg/kg gentamütsiini iga 36 või 48 tunni järgi vastavalt vere gentamütsiini tasemele 22 tunni vanuselt, on võimalik saavutada efektiivne ja ohutu gentamütsiini taseme tipp ja langus alla ≤28nädala sündinud enneaegstel vastsündinutel.

4. AB ravi kestus; Korduvad CRV määramised –AB ravi võib ohutult lõpetada 48 tunni pärast, kui külvid on negatiivsed VLBW lastel, kellel esmane CRV ja 48 tunni vanuse CRV kontsentratsioon on alla 10mg/l. Tõendid kinnitavad NICE juhise soovitusi, et **korduvaid, tihedalt ajastatud CRV kontsentratsiooni määramisi võib kasutada AB ravi juhtimiseks varase algusega infektsiooni riskiteguritega VLBW vastsündinutel.**

2. Prevention of Perinatal Group B Streptococcal Disease, Revised Guidelines from CDC, MMWR, Morb Mortal Wkly Rep. 2010; 59:RR-10**.**

CDC - Centers for Disease Control and Prevention**.**

CDC perinataalse GBS infektsiooni ennetamise ravijuhend, muudetud juhis 2010a., mille soovitused kinnitati peale analüüsi ja ülevaatamist AAP, COID, COFN poolt

3. Policy Statement-Recommendations for the Prevention of Perinatal Group B sterptococcal (GBS) Disease COMMITTEE ON INFECTIOUS DISEASES (COID) AND COMMITTEE ON FETUS AND NEWBORN (COFN)PEDIATRICS Volume 128, Number 3, September **2011.** 2011a. COID ja COFN poolt käsitletud ühisavaldus soovitustega, mis on kooskõlas CDC 2010a. GBS ravijuhisega ja sisaldas samu algoritme.

2010 a. GBS ravijuhendi (CDC, AAP) peamised muutused vastsündinute kohta:

• Muudetud algoritm vastsündinutele varase GBS riskiga haiguse raviks. Sepsise varaseks avastamiseks peaks vastsündinuid ravima selle algoritmi järgi.

-ALGORITM KEHTIB NÜÜD KÕIKIDE VASTSÜNDINUTE KOHTA!

1. Iga vastsündinu, kellel on sepsise sümptomid, peab saama täieliku diagnostilise hindamise ja AB ravi sõltuvalt tulemustest. Uuringud täielikuks diagnostiliseks hindamiseks: verekülv, täisvere analüüs (hemogramm koos 5-osalise leukotsütaarse valemi ja vereäige mikroskoopiaga, trombotsüütide arv); **Röntgen** ülesvõte rindkerestebanormaalsete respiratoorsete nähtude olemasolul; **lumbaalpunktsioon**, kui vastsündinu on piisavalt stabiilne protseduuri talumiseks ja kahtlusel sepsisele.

Ravi:1. Antimikroobne GBS vastane ravi (sisaldades i/v ampitsiliini) ja teiste mikroorganismide vastane, mis põhjustavad sepsist nagu E. Coli, jt. gramnegatiivsed patogeenid (arvestada lokaalset antibiootikumidele resistentsust)**(AII)**

2. Heas üldseisundis vastsündinud, kelle emal kahtlustati koorionamnioniiti, peavad läbima limiteeritud diagnostilise hindamise ja saama AB ravi kuni külvide tulemusteni (AII).

<u>Limiteeritud diagnostika:</u> verekülv ja täisvere analüüs sünnil (hemogramm koos 5-osalise leukotsütaarse valemi ja vereäige mikroskoopiaga, trombotsüütide arv) **ja/või 6-12 tunni vanuselt.** LP ja Rö ü/v rindkerest ei ole vajalikud. Konsultatsioon günekoloogiga, kas kahtlustatud koorionamnioniit on oluline, et vastsündinule ravi määrata **(CIII).**

3. Heas üldseisundis vastsündinud, kelle emal ei olnud koorionamnioniiti ja näidustust GBS profülaktikaks, neile peab tagama tavalise kliinilise hoolduse (CIII). Kui tekivad sepsise sümptomid, vajalik täielik diagnostiline hindamine ja AB raviga alustamine

4. Heas üldseisundis vastsündinuid, ükskõik, millise gestatsioonivanusega, kelle ema sai adekvaatse sünnitusaegse profülaktia (≥4t enne sünnitust i/v penitsilliini, ampitsilliini, tsefazoliini), peaks jälgima ≥48 tundi, ei ole vajalikud rutiinsed diagnostilised testid (BIII). Need lapsed võib koju kirjutada 24 tunni vanuselt, eeldades, et teised koju kirjutamise kriteeriumid on täidetud, eksisteerib hea ligipääs meditsiinilisele abile ja on olemas isik, kes on võimeline täitma kõiki ettekirjutatud instruktsioone koduseks jälgimiseks (CIII).Kui tekivad sepsise sümptomid, on vajalik täielik diagnostiline hindamine ja AB raviga alustamine.

5. Heas üldseisundis vastsündinuid, getstasioonivanusega ≥37 nädala ja 0 päeva , sündinud emalt, kellel oli näidustus GBS profülaktikaks,kuid kesseda ei saanudvõi see oli ebaadekvaatne,lootevesi puhkenud <18 tunni enne sünnitust, neile on vajalik jälgimine vähemallt ≥48 tundi, kuid ei ole vajalikud rutiinsed diagnostilised testid (BIII). Mõned eksperdid soovitavad 6-12 tunni vanuselt täisvere analüüsi. Kui tekivad sepsise sümptomid on vajalik täielik diagnostiline hindamine ja AB raviga alustamine.

-Heas üldseisundis vastsündinud, kelle getstasioonivanus on <37 nädala ja 0 päeva või lootevesi on puhkenud ≥18 tunni enne sünnitust, neile on vajalik limiteeritud diagnostiline hindamine ja jälgimine ≥48 tundi (BIII). Kui tekivad sepsise sümptomid, on vajalik täielik diagnostiline hindamine ja AB raviga alustamine.

<u>Järgmised olulisemad muudatused, mis tehti 2002a. juhistega võrreldes:</u>

-Algoritm kehtib nüüd kõikide vastsündinute kohta.

-**Adekvaatne sünnitusaegne GBS profülaktika antibiootikumidega, milleks on:≥4t enne sünnitust i/v penitsilliini, ampitsilliini, tsefazoliini (AIII).** Kõiki teisi ravimeid või ravikestusi käsitletakse, kui ebaadekvaatset GBS profülaktikat arvestades vastsündinuid.

-**Heas üldseisundis vastsündinuid, kelle emal oli näidustus GBS profülaktikaks aga ei saanud seda või see oli ebaadekvaatne:**

-kui gestatsioonivanus ≥37 nädala ja 0 päeva, lootevesi puhkenud <18 tunni enne sünnitust, vajalik jälgimine ≥48 tundi, ei ole vajalikud rutiinsed diagnostilised testid (BIII). Mõned eksperdid soovitavad hemogrammi koos 5-osalise leukotsütaarse valemi, vereäige mikroskoopiaga, trombotsüütide arv 6-12 tunni vanuselt.

-heas üldseisundis vastsündinud, gestatsioonivanus **<37 nädala** ja 0 päeva või lootevesi puhkenud ≥18 tunni enne sünnitust, neile on vajalik **limiteeritud diagnostiline hindamine ja jälgimine ≥48 tundi (BIII).** <u>Limiteeritud diagnostika:</u> verekülv sünnil, hemogramm koos 5-osalise leukotsütaarse valemi, vereäige mikroskoopiaga, trombotsüütide arv sünnil ja/või 6-12 tunni vanuselt.

- **Heas üldseisundis vastsündinuid, gestatsioonivanuses 35-36näd., kelle emad said adekvaatse sünnitusaegse profülaktika, ei vaja rutiinselt diagnostilist hindamist (CIII).**

4.Prevention and Management of Infants With Suspected or Proven Neonatal Sepsis
MT. Brady, Richard A. Polin, PEDIATRICS Volume 132, Number 1, July **2013**
Kokkuvõttvad soovitused: 2010 CDC muudetud ravijuhisest ja COFN 2012 kliinilises aruandes avaldatud ravijuhistest
1. Vastsündinud sepsise kliiniliste tunnustega peavad saama AB ravi laiatoimespektriga antibiootikumidega
2. Heas üldseisundis enneaegsed ja ajalised vastsündinud, kelle emal oli kahtlus koorionamnioniidile: sünnil verekülv, täisvere analüüs valemiga ±, CRV 6-12 tunni vanuselt, AB ravi laiatoimespektriga antibiootikumidega
3. Heas üldseisundis vastsündinud ≥37 nädala, kelle emal ei olnud kahtlust koorionamnioniidile, aga oli näidustus sünnitusaegseks antibakteriaalseks profülaktikaks (IAP), kuid ei saanud vähemalt 4t enne sünnitust penitsiliini, ampitsilliini või tsefazoliini:
a) 2010 GBS juhis ja 2012 COFN on nõus, et kui laps on heas seisundis võib jälgida lisatestideta, kui lootevesi on puhkenud<18 tunni. **COFN juhises enneaegseid gestatsioonivanuses 35-36 nädalat võib samamoodi ravida, kui füüsiline läbivaatus on normaalne**
b) kui lootevesi on puhkenud ≥18 tunni ja IAP on ebaadekvaatne, 2010 juhis soovitab limiteeritud hindamist (verekülv, täisveri valemiga sünnil ja 6-12 tunni vanuselt) ja haiglas jälgimist 48 tunni jooksul). **COFN juhis soovitab haiglas jälgimist 48 tunni jooksul samadel asjaoludel (ilma lisa testide või külvideta).** Kui jälgimine pole võimalik, siis COFN soovitab laboratoorseid teste.
4. Heas üldseisundis vastsündinud <37 nädala, kelle emal ei olnud kahtlust koorionamnioniidile, kuid kellel oli näidustus IAP ja ei saanud adekvaatset profülaktikat, 2010 juhis soovitab limiteeritud hindamist (verekülv, täisveri valemiga) ja haiglas jälgimist 48 tunni jooksul. **COFN juhis soovitab limiteeritud hindamist, kuid mitte verekülvi võtmist, kui ei alustata antibiootikum raviga ebanormaalste laboratoorsete näitajate tõttu.**
5. 2010a.Juhendis ei määrata AB ravi kestust. COFN soovitab AB ravi kestust sõltuvalt laboratoorsetest näitajatest. **Heas üldseisundis vastsündinutele ilma tõenditeta bakteriaalsele infektsioonile i/v laiatoimespektriga AB ravi mitte kauem kui 48 tundi. Väikestel enneaegsetel võib mõnel juhul jätkata AB raviga kuni 72 tundi, kui oodatakse bakteriaalsete külvide vastuseid.**

Süstemaatilised ülevaated

Kokkuvõte süstemaatilistest ülevaadetest, randomiseeritud uuringutest, prospektiivsetest uuringutest
Infektsiooni riskiteguritega enneaegsete vastsündinute ravitulemi parandamiseks profülaktilise antibakteriaalse ravi kasutamise kohta penitsilliini või ampitsilliini ja gentamütsiiniga, ravi kestuse ja lõpetamise näidustusete kohta, oli vastavalt otsingukriteeriumitele kättesaadavad:
-2012.a. avaldatud 1 kliiniline aruanne ravijuhistega AAP – (Ameerika Pediaatria Akadeemia) ja COFN –(Loote ja Vastsündinu Komitee) poolt**:** praktilisete ja tõenduspõhiste soovitustega varase algusega sepsise kahtluse või kinnitunud sepsise raviks, käsitleb soovitusi/algoritme ajalistele ja enneaegsetele vastsündinutele.
-Viimase 5. aasta jooksul antud teema kohta avaldatud 5 ülevaateartikklit: 2012, 2013, 2013, 2014, 2014 aastal; -1 süstemaatiline ülevaade/metaanalüüs 2015a.

-5 uuringut enneaegsetel vastsündinutel: 2 RCT uuringur 2014, 2010a.; prospektiivnerandomiseeritud uuring 2011a.; retrospektiivne kohort uuring 2011a.; randomiseeritud uuring 2010a. (open label cluster randomized equivalence study).

Viited

Kokkuvõtte (abstract või kokkuvõtlikum info)	**Viide kirjandusallikale**
COFN 2012 kliiniline aruanne ravijuhenditega, kokkuvõte soovitustest: **Vastsündinute ravi tõestatud või kahtlustatava varase algusega bakteriaalse sepsise korral.** -Vastsündinu sepsis on peamine haigestumise ja surma põhjus enneaegsete populatsioonis.Vastsündinuid identifitseeritakse varase algusega sepsisele sageli perinataalsete riskitegurite järgi, mis on sensitiivsed, kuid mitte spetsiifilised. Diagnostilistel testidel on vähene positiivne ennustav täpsus neonataalsele sepsisele. Sageli ravitakse heas üldseisundis lapsi pikemaaegselt, isegi kui bakteriaalsed külvid on negatiivsed. -Diagnostilised testid varase infektsiooni identifitseerimiseks (mitte verekülv ja liikvori külvid) on vajalikud, identifitseerimaks vastsündinud, kellel on madal sepsise tõenäosus, mitte ei identifitseeri lapsi, kes on infitseeritud. - Bakterieemia adekvaatseks hindamiseks enne AB ravi alustamist on verekülvi jaoks vajalik võtta 1ml verd (0,5ml on ebapiisav kogus), kui kasutatakse pediaatrilisi verekülvi pudeleid. Külve ei ole vaja võtta kehapindadelt, maoaspiraadist ja uriinist – ei oma väärtust varases sepsise diagnostikas. -Optimaalne ravi varase algusega sepsise kahtlusel on laiatoimespektriga antibiootikumid (ampitsilliin ja aminoglükosiidid), kui patogeen on identifitseeritud, siis kitsatoimega antibiootikumid. -**Hiljutiste uuringute andmetel, enneaegsetel vastsündinutel on leitud seos prolongeeritud empiirilise AB ravi(kestusega ≥5 päeva) kasutamisega laiatoimespektriga antibiootikumidega hilise sepsise, nekrootilise enterokoliidi ja suremuse kõrgema riski vahel. Nende riskide vähendamiseks, peab empiirilise AB ravi lõpetama 48 tunni jooksul kliinilisetes situatsioonides, kus sepsise tõenäosus on madal.** Kliinilise aruande eesmärk on anda praktilisi ja tõenduspõhiseid soovitusi varase algusega sepsise kahtluse või kinnitunud sepsise raviks. **Asümptomaatilise gestatsioonivanuses <37 nädala enneaegse vastsündinu hindamine sepsise (algusega alla ≤3 esimese elupäeva) riskitegurite suhtes:** **Riskitegurid:** koorionamnioniit või lootevesi puhkenud ≥18 tunni enne sünnitust või ebaadekvaatne sünnitusaegne GBS profülaktika. **Vajalikud diagnostilised testid:** verekülv ja täisvere analüüs sünnil, CRV 6-12 tunni vanuselt. **Ravi:** laiatoimespektriga antibiootikumid (ampitsilliin ja aminoglükosiidid, tavaliselt gentamütsiin), kui patogeen identifitseeritud, siis kitsatoimega AB. **Ravi: a)verekülv positiivne** – jätka AB ravi, lumbaalpunktsioon on	**5.FROM THE AMERICAN ACADEMY OF PEDIATRICS, CLINICAL REPORT** **Management of Neonates With Suspected or Proven Early-Onset Bacterial Sepsis** Polin RA, and the COMMITTEE ON FETUS AND NEWBORN **(COFN)** PEDIATRICS Volume 129, Number 5, May **2012**

näidustatud, kui verekülv positiivnevõi onkliiniliste sümptomite alusel tugev kahtlus sepsisele, vastus ravile on halb, esineb bakterieemia laboratoorsetel andmetel **b) verekülv negatiivne, lapse üldseisund hea, laboratoorsed analüüsid ei ole normis** – jätka AB ravi kui ema sai antibiootikume sünnitustegevuse ja sünnituse ajal **c) verekülv negatiivne, laps heas üldseisundis, laboratoorsed näitajad normis – lõpeta AB ravi.**	
Uuendatud GBS ennetamise ja ravi strateegia perinataalperioodis lähtudes hiljutistest Ameerika Ühendriikide, Austraalia ja Uus-Meremaa ravijuhistest **1. Igal vastsündinul, kellel on sepsise sümptomid** (hingamishäired, apnoe, kahvatus halva perifeerse perfusiooniga, palavik ≥ 38°C või ebastabiilne temperatuur ja atsidoos), **teostada täielik diagnostiline hindamine** (täisvere analüüs valemiga, verekülv, külv liikvorist, näidustusel röntgen ülesvõte rindkerest) **ja alustada AB ravi laiatoimespektriga antibiootikumidega (näiteks penitsilliin ja gentamütsiin) oodates külvide vastuseid** (Verani et al 2010,Vergnano et al 2011,Campbell 2004). Kliinilised sümptomid on kõrge sensitiivsusega sepsise näitajad (Escobar et al 2000). **2.** CDC juhised soovitavad kõikidele heas üldseisundis vastsündinutele,kes on sündinud **koorionamnioniidi kahtlusega** emalt läbi viia limiteeritud diagnostilise hindamise ja alustada AB raviga külvide vastuste saabumiseni., **Uus-Meremaa konsensusjuhis soovitab hoolikat jälgimist, uuringud ja ravi on vajalikud ainult kui vastsündinul on sepsise sümptomid** **3. GBS positiivsed emad, kes on saanud sünnitusaegset AB profülaktilist ravi –nende vastsündinud võib koju kirjutada 24 tundi peale sündi tingimusel, et nad on tervishoiutöötaja hoolika jälgimise all** (kliiniliselt varane sepsis manifesteerub tavaliselt esimese 24 tunni jooksul (Escobar et al 2000, Bromberger et al 2000). **4. Ebaadekvaatse AB profülaktika korral emade vastsündinuid tuleks jälgida haiglas 24 tunni jooksul.** On ebatõenäoline, et rutiinselt tehtavad laboratoorsed testid (täisveri või CRV) parandavad sepsise avastamist võrreldes kliinilise läbivaatusega (Escobar et al 2000). **5. CDC soovitab heas üldseisundis ajalisi vastsündinuid riskiteguritega varasele infektsioonile** jälgida haiglas 48 tunni jooksul, samas kui riskiteguritega enneaegseid või ≥18 tunni puhkenud lootevee korral, teha täisvere analüüs valemiga ja võtta verekülv. Uus-Meremaa juhis soovitab aga ajalisi heas üldseisundis vastsündinuuid haiglas jälgida 24 tundi.	**6.Review article** **Prevention of neonatal group B streptococcus disease in the 21st century** Clifford V, Garland SM, Grimwood K. Journal of Paediatrics and Child Health,48,808-815**, 2012**
2. Soovitused ajalistele ja hilisenneaegsetele vastsündinutele (>34rn.), kellel on riskperinataalseks bakteriaalseks infektsiooniks,muudetud ja ülevaadatud juhised Sveitsi Neonatoloogia Ühingu ja Sveitsi pediaatrilise infektsioonhaiguste grupi poolt 2013aastal. **<u>Kokkuvõte:</u>** **Kliinilised süptomid varase algusega sepsisele (EOS) on mittespetsiifilised, varieeruvad, võivad esialgu puududa:** tahhüpnoe, respiratoorne düstress, apnoe; tahhükardia, bradükardia, halb perifeerne perfusioon (kapillaartäitumus >3 sekundi), laigulisus;	**7.Review article** **Recommendations for term and late preterm infants at risk for perinatal bacterial infection**

temperatuuri ebastabiilsus (hüpertermia >38 kraadi C või hüpotermia <36.0 kraadi C); letargia, erutatavuse tõus, lihastoonuse muutused või lõtvus; oksendamine, toitmisprobleemid. **Kõiki vastsündinud kliiniliste sümptomitega, mis viitavad neonataalsele infektsioonile tuleb ravida empiirilise AB raviga, kui verekülv on võetud.** **Riskitegurid varase algusega sepsisele:** ema GBS kolonisatsioon(vaginaalne/rektaalne väljakülv), bakteriuuria või infektsioon käesoleva raseduse ajal; koorionamnioniit (ema palavik >38C lisaks vähemalt 2 sümptomit – leukotsütoos >15G/l, loote tahhükardia (>160xmin), emaka hellus/valilikkus, lõhnav tupevoolus); PROM >18 tunni, EA sünnitus <37GN, eelmisel lapsel invasiivne GBS infektsioon; ühel lootel kahtlus infektsioonile mitmikraseduse korral. **Vastsündinuid, kelle emadel oli vajadus sünnitusaegseks AB profülaktikaks, on vajalik jälgida 48 tundi postnataalselt**. **Tavaliselt, perinataalse infektsiooni korral, 90% juhtudest tekivad sümptomid esimese 24-48tunni jooksul.** **Kui intrapartum profülaktika emal jäi saamata** või ebaadekvaatne, alla 4tunni enne sünnitust, siis vastsündinul on infektsioonirisk ja ta vajab kliinilist jälgimist. **Riskiteguritega asümptomaatilisi vastsündinuid tuleks jälgida 48 tunni jooksul, monitoorida elulisi näitajaid iga 4 tunni tagant:** hingamine, temperatuur, perifeerne perfusioon, jume. **Plaanilise keisrilõike korral** (kui lootevesi ei ole puhkenud või ei ole kontraktsioone) – ei ole vastsündinu postnataalne jälgimine vajalik (sõltumata ema GBS staatusest). **Koorionamnioniit emal:** vastupidiselt täiendatud CDC juhiste soovitustele 2010a., **me ei soovita empiirilist antibakteriaalset ravi asümptomaatilistele vastsündinutele, kelle emadel oli koorionamnioniit. Soovitav jälgimine 48 tundi, nagu teistele asümptomaatiliste infektsiooni riskiteguritega lastele. See soovitus on kooskõlas Austraalia ja Uus Meremaa (2012) ja AAP 2012 juhistega (Clinical Report 2012) vasündinute raviks riskiga varase algusega sepsisele.** **Kui ema GBS staatus teadmata, emale on vajalik intrapartum profülaktika, last tuleks jälgida postnataalselt 48 tundi**, **kui on lisa riskitegurid:** (EA sünnitus <37näd., PROM >18 tunni, koorionamnioniidi kliinik). **Lumbaalpunktsioon on** alati vajalik, kui verekülv on positiivne ja/või kriitiliselt haigetel lastel. **Ravi neonataalse infektsiooni kahtluse korral:** aminoglükosiid (amikatsiin või gentamütsiin) kombineerituna amoksitsiliiniga i/v on standard empiiriline AB ravi. I elunädala doosid vastsündinule: **gentamütsiin 4-5mg/kg/dosi ja amoksitsilliin 50-100mg/kg/dosi iga 12 tunni järgi**. Aminogükosiidide korral on vajalik terapeutilise ravimi kontsentratsiooni jälgimine. **AB ravi kestus:** kliiniline sümptomatoloogia, negatiivne verekülv ja laboratoorsed näitajad (akuutse faasi reaktandid), otsustada kas on edasi vaja ravi üle 48 tunni. **Erinevad uuringud** (Alexander et al 2011, Cotton et al 2009, Kuppala et al 2011) **on näidanud, et prolongeeritud**	**Revised guidelines of the Swiss Society of Neonatology in collaboration with the Paediatric Infectious Disease Group of Switzerland** (PIGS): modified version based on a previous publication in the Journal of the Swiss Society of Paediatrics [1]* *Stocker M, Berger C, McDougall J, Giannoni E Taskforce for the Swiss Society of Neonatology and the Paediatric Infectious Disease Group of Switzerland* **Review article,** September **2013**, doi:10.4414/smw.2013.13873 **Cite this as:** Swiss Med Wkly. **2013**;143:w13873

AB ravi kasutamine >5 päeva tõstis suremust ja sagedasemat enterokoliidi esinemissagedust enneaegsetel vastsündinutel, mis rõhutab vajadust lõpetada empiiriline AB ravi tõestatud infektsiooni puudumisel (negatiivne verekülv ja negatiivsed akuutse faasi reaktandid) nii vara kui võimalik, hilisemalt 48-72 tunni pärast.	
Kokkuvõte: 2010a. CDC juhise neonataalset algoritmi ei ole üldiselt/kogu maailmas aktsepteeritud ja seepärast soovitatakse erinevaid algoritme.Kuna kõik lähenemisviisid haiguse perventsiooniks on siiski mittetäielikud, optimaalne algoritm GBS varase algusega infektsiooni raviks on ikka veel puudulik, siis paranenud diagnostiliste meetmete areng riskilaste eristamiseks võib kaasa aidata paremale kliinilisele lähenemisviisile. **Queensland Sünnitusmaja ja Neonataalne kliiniline juhiste programm** (Maternity and Neonatal Clinical Guidelines Program) **varase infektsiooni preventsiooni juhises 2010a., soovitab rakendada empiirilist antibakteriaalset ravi <37 rasedusnädala sündinud enneaegsetele, kui emal oli puudulik sünnitusaegse AB profülaktika** [2010]. (COFN 2012a. soovitab ka ravida, CDC juhis 2010a. ei soovita ravida). Üks peamisi varase algusega sepsise riskitegur on madal gestatsioonivanus (Mukhopadhyay, Puopolo, 2012). Ühes populatsioonipõhises jälgimise programmis aastatel 2005-2008 (USA-s 4-s CDC Active Bacterial Core surveillance sites) leiti, et varase sepsise sagedus0.77 juhtu /1000 elussünni kohta, vähenes 0.5juhtu/1000 elussünni kohta >37rasedusnädala sündinud vastsündinutel, võrreldes 3.0/1000 elussünnikohta<37rn. Enneaegsetel (Weston et al 2011). Kuigi varase sepsise risk on kõrgem väga madala sünnikaaluga vastsündinute hulgas, isegi keskmine enneaegsus on seotud suurenenud riskiga sepsisele (Mukhopadhyay, Puopolo, 2012). Vastsündinu haigestumus hilisenneaegsetel võrreldes ajaliste vastsündinutega, mida uuriti retrospektiivses kohortuuringus 18 aasta jooksul, leiti, et hilisenneaegsetel sepsise sagedus 1000 elussünnikohta oli 0.5, 0.4 ja 0.2 gestatsioonivanuses 34., 35., 36. nädalat võrreldes 0.1 GV 39. nädalal sündinud ajaliste vastsündinutega ($p<0.001$) (McIntire, Leveno 2008). Samasugune varase sepsise esinemissagedus leiti vaatluslikus kohortuuringus enneaegsetel gestatsioonivanusega 34-36n. aastatel 1996-2007, 0.4% ja 0.5% (Cohen-Wolkowiez, 2009). 2011. aastast kasutame lokaalset algoritmi, mis baseerub CDC 2010a. juhisele, v.a. asümptomaatilistele lastele, kelle ema sai puuduliku profülaktilise AB ravi, <37rasedusnädala sündinud enneaegsetel või PROM ≥18 tunni, **neile rakendame limiteeritud diagnostilise hindamise** (nagu CDC 1010 – verekülv ja täisveri valemiga sünnil ja/või 6-12 tunni vanuselt) ja **empiirilise AB ravi, kuni infektsioon on välistatud** (negatiivne verekülv, normaalsed laboratoorsed näitajad, sepsise kliiniliste tunnuste puudumine).	**8.Review article** **Which is the optimal algorithm for the prevention of neonatal early-onset group B streptococcus sepsis?** Tzialla C, Borghesi A, Longo S, Stronati M Early Human Development 90S1 **(2014)** S35–S38
Kokkuvõte Ülevaates käsitletakse varase ja hilise vastsündinu sepsise epidemioloogiat, empiirilist antibakteriaalset, antifungaalset ravi, AB ravi kestust, soovitatavaid AB doose, jne. **Neonataalne sepsis põhjustab kõrget haigestumust ja suremust,**	**9.Review article** **Considerations in the**

seetõttu on vajalik viivitamatu AB ravi alustamine peale külvide võtmist. Soovitav on alustada ravi kombinatsioonis ampitsilliini ja aminoglükosiidiga. **Meningiidi kahtlusel, ampitsiliini ja tsefotaksiimiga**. Tekitaja identifiteerimisel jätkata ravi kitsatoimespektriga antibiootikumiga. Vajalik on ravimi terapeutiline monitooring vastsündinutele, kes saavad ravi vankomütsiini või aminoglükosiidiga (k.a. gentamütsiiniga). Invasiivse seeninfektsiooni korral on ohutu kasutada liposomaalset amfoteritsiin B, efektiivne renaalse puudulikkusega patsientidel või konventsionaalsest amfoteritsiin B põhjustatud toksilisuse korral.Seenevastane profülaktika flukonazooliga on dramaatiliselt vähendanud neonataalset invasiivset seeninfektsiooni ja parandab neuroloogilisarengulisi kaugtulemusi ravitud lastel. Paljud suured, mitmekeskuselised uuringud, uurivad ohutust ja efektiivsust suukaudse laktoferriini kasutamisest immuunprofülaktilise ravina vastsündinu sepsise preventsiooniks. **Kõige sagedasem patogeen, mis on seotud varase algusega sepsisegavastsündinul on B-grupi streptokokk (GBS) ja Escherichia coli, mis koos moodustavad peaaegu 70% infektsioonidest** (Stoll et al 2011). Veidi vähem varase sepsise põhjustajaks on*Streptococcus viridans*, *Enterococcus species*, enteerilised gramnegatiivsed batsillid ja *Listeria monocytogenes*. Ema vaginaalne kolonisatsioon *Staphylococcus aureusega* võib põhjustada vertikaalset bakterite ülekannet raseduse ajal. Neonataalne kandideemia võib esineda esimesel 7 elupäeval (Kaufman et al 2003). **<u>Antibakteriaalne ravi</u>** **Sepsise kahtlusel või tõestatud sepsise korral peale külvide võtmist alustada empiirilise i/v antibakteriaalse raviga, tavaliselt kombinatsioonis penitsilliini ja aminoglükosiidiga (gentamütsiiniga)** (Klein 2001). **Ampitsilliin** on eelistatud oma toime poolest grampositiivsetele infektsioonidele, nagu GBS, L. Monocytogenes, ja mõningane toime gramnegatiivsetele bakteritele. **Gentamütsiin** lisatakse toime tõttu paljudele gramnegatiivsetele bakteritele, mis on tavaliselt varase sepsise põhjustajad (E. Coli, Enterobacter species). **Stafülokokkinfektsiooni kahtlusel, peab ravi alustama penitsillinaas-resistentse penitsiliiniga või vankomütsiiniga**. Linezoliidil on ka aktiivsus grampositiivsete tekitajate vastu, k.a. MRSA, vankomütsiin resistentsed enterokokid ja penitsillinaas-resistentne *Streptococcus pneumoniae (Dotis et al 2010)*. Vähe on uuringuid vastsündinul linezoliidi kohta, 1 randomiseeritud kontrolluuring näitas, et **linezoliid oli võrdselt efektiivne vankomütsiiniga grampositiivsete infektsioonide ravis ja oli seotud vähem ravimist põhjustatud kõrvaltoimetega** (Deville et al 2003). <u>Ravimitele multiresistentsete tekitajate korral nagu Klebsiella pneumoniae, laiatoimespektriga β-laktamaasi produtseeriva Enterobacteri korral, võib kaaluda imipeneemi ja meropeneemi kasutamist</u>(Clissold et al 1987). **Meningiidi kahtlusel** või tõendatud meningiidi korral, kasutada **eelistatult tsefotaksiimi**, kuna tal on väga hea penetratsiooni liikvorisse. Kasutada empiiriliselt ainult neuroloogilistel juhtudel, kuna	**Pharmacologic Treatment and Prevention of Neonatal Sepsis** Stockmann C, Spigarelli MG, Campbell SC, Constance JE, Courter JD, Thorell EA, Olson J, Sherwin C.M. T. Pediatr Drugs **(2014)** 16:67–81

uuringutega on näidatud, et esineb tõusnud risk surmale ja invasiivsele kadidiaasile (Clark et al 2006, Cotten et al 2006). **Verekülvide võtmine on kuldne standard bakterieemia avastamiseks** (NICE juhis, 2012). Verekülvid ei ole 100% sensitiivsed, mis võibolla tingitud antenataalsest AB profülaktikast, väikesest verekogusest analüüsi võtmisel enneaegsetel, transitoorsest või intermitteeruvast bakterieemiast. 96% verekülvidest muutuvad positiivseks esimese 48 tunni inkubatsiooniperioodi jooksul. **<u>Soovitatavad ravimidoosid</u>** vt. Tab.3.(vt. viited), linesoliid, vankomütsiin. **Gentamütsiin** i/v, vanus ≤7 päeva, kaal <2kg 5 mg/kg/dosi, 48 tunni järgi, Kaal ≥2kg, 4 mg/kg/dosi, 24 tunni järgi; **Ampitsilliin** i/v, vanus ≤7p., kaal <2kg, 50mg/kg/dosi 12 tunni järgi, Kaal ≥2kg,50 mg/kg/dose 8 tunni järgi **Tsefotaksiim** i/v, vanus ≤7 päeva, kaal <2kg ,50 mg/kg/dose 12 tunni järgi Kaal ≥2kg, 50 mg/kg/dose 12 tunni järgi. **Ravi kestus –** soovitav 7-10 päeva bakterieemia korral fokaalse infektsiooni koldeta. GBS meningiidi korral või on gramnegatiivsed enteerilised batsillid, AB ravi kestus <21 päeva, või 14p. peale steriilset liikvori külvi (Red Book, 2012).	
2015a. süstemaatilises ülevaates ja metaanalüüsis analüüsiti varase algusega vastsündinu infektsiooni esinemissagedust bakteriaalse infektsiooniga või kolonisatsiooniga emadelt, hõlmatud oli 122 uuringut, 7 uuringut (5.7%) oli väga kõrge neonataalse suremusega kohtadest. Uuringute vahel esines märkimisväärne heterogeensus, andes erinevaid definitsioone infektsioonile (laboratoorselt kinnitunud, kliinilised sümptomid), kolonisatsioonilejainfektsiooniriskiteguritele. Vastsündinutel, kelle emadel oli laboratoorseltlt kinnitunud bakteriaalne infektsioon (külv või PCR kinnitas bakterieemiat-, amnioniiti-, kuseteede infektsiooni-, koorionamnioniiti või oli kliiniline koorionamnioniit) neil esines varase algusega laboratoorselt kinnitunud infektsioon 17.2% (95%CI 6.5-27.9). Kolonisatsiooniga emade vastsündinutel laboratoorselt kinnitunud infektsiooni esinemine oli 0% (95% CI 0.0-0.0). Kolonisatsiooniga emade vastsündinutel esines vastsündinu kehapinna kolonisatsioon vahemikus 30.9-45.5% sõltuvalt tekitajast. Riskiteguritega emade vastsündinutel esines laboratoorselt kinnitunud infektsioon vahemikus 2.9-19.2% sõltuvalt riskitegurist. Riskitegurid uuringus: PROM - enne sünnitustegevuse algust ≥37 rasedusnädala lootevee puhkemine, PPROM - <37 rasedusnädala lootevee puhkemine enne sünnitustegevuse algust, ROM –lootevee puhkemise kestus ≥18-24 tunni või mitte defineeritud. **<u>Järeldused:</u> infektsiooniga emadel ja riskiteguritega emadel on varase algusega vastsündinu infektsiooni esinemissagedus kõrge.** Vajalikud on kõrgema kvaliteediga uuringud, et täpsemalt hinnata varase infektsiooni esinemissagedust riskiga vastsündinutel.	**10. Prevalence of early-onset neonatal infection among newborns of mothers with bacterial infection or colonization: a systematic review and meta-analysis** Chan GJ, Lee ACC, Baqui AH, Tan J, Black RE BMC Infectious Diseases **(2015)** 15:118
Ülevaate eesmärgiks oli esitada käesolevad seisukohad ja tõendid, mis mõjutavad klinitsistide valikuid empiirilise antibakteriaalse	**11. Review article**

ravi kestuselenegatiivsete külvide korral. Hiljutised andmed retrospektiivsetest uuringutest näitavad potentsiaalset kahjulikkust pikemaaegse empiirilise AB ravi kestuse korral, kui külvid on negatiivsed. **Esinevad epidemioloogilised tõendid suuremast suremusest ja haigestumisest enneaegsetel vastsündinutel negatiivsete külvide korral ja pikemaaegse empiirilise AB ravi korral, tõusutendentsiga on antimikroobne resistentsus tavaliste patogeenide hulgas (k.a. E.coli, 2/3 varase sepsise tekitajatest isoleeritud E.coli on ampitsiliin resistentne)** (Weston et al 2011, Stoll et al 2011, Cotten et al 2009, Bizzarro et al 2008, Kuppala et al 2011). Kohortuuringud viitavad laialt kasutatavate testide ajastamisele, mida kasutatakse varase sepsise riski hindamiseks ennustava väärtuse tõttu ja testidele 24-48 tunni vanuselt, mille alusel võib ohutult AB ravi lõpetada. **<u>Kellel võib jätkata 48tunni vanuselt empiirilist AB ravi?</u>** **-vastsündinutel, kellel külvid on positiivsed** jätkata AB ravi, kestus baseerub tõendatud spetsiifilise mikroobi tundlikkusel AB-le (2010,CDC) **-vastsündinutel kliiniliste sümptomitega, mis kestavad rohkem kui I elupäeva,** peab rakendama pikemt AB ravi, mida tõsisemad on sümptomid, (mehhaanilise ventilatsiooni-, vasopressorite vajadus) seda tõenäolisemad on positiivsed külvid (Escobar et al 2000, uuring EA ≥2000g) **-AB ravi jätkamine isegi negatiivsete külvide korral pidevalt haigetele vastsündinutele,** mis on osaliselt tingitud võimalikest valenegatiivsete steriilsete vere- või liikvori külvide esinemisest. Kasutatakse BACTEC süsteeme verekülvide jaoks, milles suure tõenäosusega on bakter identifitseeritav 1ml materjalist (Garcia-Prats et al 2000). <u>Esineb ka situatsioone, kus madal mikroobi kontsentratsioon võib põhjustada märkimisväärseid probleeme, kuid võib olla mitte määratav, kui analüüsitava verekogus on liiga väike</u> (Schelonka et al 1996). Enne külvide võtmist AB ravi kasutamine võib mikroobi identifitseerimist takistada külvimeetodiga, kuigi osad uuringud väidavad, et mikroob on määratav isegi, kui on eelnevalt emale kasutatud sünnitusegaset AB profülaktikat (Garcia-Prats et al 2000). **<u>Kellel AB ravi lõpetada 48tunni vanuselt, kas hemogramm valemiga/täisvere analüüs aitab?</u>** **- vastsündinutel, kellel alustati empiirilise AB raviga varase infektsiooni kahtluse tõttu, kellel külvid on steriilised, kliiniliselt infektsiooni tunnusteta ja normaalsed skriining laboratoorsed testid, tuleb lõpetada AB ravi ≤48t/vanuselt.** -ühekeskuselises uuringus, üle 3000 vastsündinu, kes suunati intensiivravi osakonda, kellel oli verekülv võetud 1.elutunnil, täisvere analüüs 1.elutunnil ja korduvalt 8-12tunni vanuselt; ühelgi 1539 vastsündinust (49%), kellel oli 2 normaalset ebaküpsete neutrofiilide ja küpsete neutofiilide üldarvu suhet (I:T suhet) ja negatiivne verekülv 24 tunni vanuselt, järgnevalt ei tekkinud sepsist (Murphy et al, 2012). Seega, **kui varased testid on normis, külv on steriilne, vastsündinu on heas üldseisundis, peab antibiootikumid lõpetama.**	**Duration of empirical antibiotic therapy for infants suspected of early-onset sepsis** Cotten MC, Smith PB. Curr Opin Pediatr. **2013** April ; 25(2): 167–171.

<u>Kokkuvõte:</u> esinevad piiratud tõendid, et toetada universaalset lähenemist empiirilise AB ravi kestuse kohta, kui külvid on negatiivsed, aga otsuseid on vaja kogu aeg teha. **<u>Käesolevad ravi kestuse soovitused ajalistele/hilisenneaegsetele vastsündinutele, kellel oli alustatud empiirilise antibakteriaalse raviga, kahtlusega varase algusega sepsisele, kui külvid on steriilsed 48 tunni vanuselt ja lisaks:</u>** 1. Kliinilised infektsiooni tunnused kestusega üle 24 tunni: ravi 7 päeva 2. Kliinilised infektsiooni tunnused esialgu puuduvad, kuid ilmnevad postnataalselt peale esimest 4 elutundi ja persisteeruvad üle 24 tunni: ravi 7 päeva 3. Analüüsid võetud riskitegurite tõttu, kliinilised sümptomid puuduvad, esialgne (4 postnataalsel tunnil) laboratoorne täisvere analüüs normis: ravi 48 tundi 4. Analüüsid võetud riskitegurite tõttu, kliinilised sümptomid transitoorsed (lahenesid 8 tunni jooksul), esialgne täisvere analüüs patoloogiline: võta CRV 24t ja 48t vanuselt. Kui CRV väärtused madalad, kliiniline läbivaatus püsib nomis, lõpeta antibiootikumid 48 tunni vanuselt.	
Randomiseeritud kontrolluuring, kus võrreldi kahtlusega varasele sepsisele alustatud empiirilise antibakteriaalse ravi ebaõnnestumist 3 või 5 päevase kestusega üle 1500g ja/või gestatsioonivanusega>34 nädala enneaegsetel vastsündinutel. Uuringus osales 60 EA last, kes kliiniliste sümptomitega sepsisele said raviks ampitsilliini + amikatsiini 2-s intensiivravi osakonnas. Peale 72 tundi, kui külvid olid negatiivsed ja sümptomid lahenenud, nad randomiseeriti 2 gruppi 3 või 5 päevase AB ravikestusega. Ravi loeti ebaõnnestunuks, kui sepsise sümptomid ilmusid uuesti 2 nädala jooksul peale ravi lõpetamist järelkontrolli perioodil. Ühel lapsel 3p. ravigrupis esines ravi ebaõnnestumine võrreldes ravi mitte ebaõnnestumisega 5p. ravikestuse korral (P=0.5). Ei esinenud tõsist kahju empiirilise AB ravi tõttu. **Kokkuvõte: selle uuringu tulemused näitavad - ei ole tõendeid, et ravi ebaõnnestumine erineks 3- ja 5 päevase antibiootikumravi kestuse korral kahtlusel varase algusega mittekomplitseeritud neonataalsele sepsisele hilisenneaegsetel ja ajalistel vastsündinutel.**	**12.3-Day versus 5-Day Course of Intravenous Antibiotics for Suspected Early Onset Neonatal Sepsis: A Randomized Controlled Trial** Pasha YZ, Ahmadpour-Kacho M, Behmadi R, Jahangir T. Iran J Ped, Vol 24 (Number 6), Dec **2014**,pp: 673-678
2011a. retrospektiivses kohortuuringus osales 365 väga väikese sünnikaaluga ≤1500g ja ≤32 rasedusnädala enneaegset last, kes elasid esimese elunädala ilma sepsise ja nekrootilise enterokoliidita. 3-keskuseline uuring, teostati aastatel 2000-2004. Uuriti, kas esines hilisemat sepsist, NEK-i ja surma peale prolongeeritud empiirilise AB ravi rakendamist (≥ 5päeva) esimesel elunädalal. Limiteeritud AB raviks loeti 1-4p. **Tulemused:** 365 enneaegset, kes elasid esimesed 7 päeva ilma sepsise ja NEK-ta, 36% said prolongeeritud initsiaalset empiirilist AB ravi (ampitsilliinija gentamütsiiniga; kasutati 7 p. jooksul ka teisiantibiootikume-klindamütsiin 1.4%, amfoteritsiin B 1%, naftsilliin 0,8%, tsefotaksiim 0.8%), mis oli sõltumatult seotud hilisema lõpptulemusega: **hiline sepsis** (odds ratio [OR] 2.45, 95% confidence interval [CI] 1.28–4.67) ja **kombinatsioon hilisema sepsise, NEK-i, või surmaga**(OR 2.66, 95% CI 1.12–6.3). Pikemalt ravi saanud lapsed	**13.Prolonged Initial Empirical Antibiotic Treatment is Associated with Adverse Outcomes in Premature Infants** Kuppala VS, Meinzen-Derr J, Ardythe L, Morrow AL, Schibler KR.

olid sagedamini sündinud koorionamnioniidiga-, ja sünnitusaegset profülaktikat saanud emalt, väiksema sünnikaaluga, väiksema gestatsioonivanusega, 5min. Apgari hinne alla 6. palli, vajasid intubatsiooni respiratoorse düstress sündroomi tõttu, mehhaanilist ventilatsiooni ja kõrgemat hapniku kontsentratsiooni võrreldes limiteeritud AB grupi lastega. 21% -l (71 last) diagnoositi **hiline sepsis;** 4,5%-l (17 lapsel) **NEK**; 5,5% lastest (20 last) surid. **Sepsis, NEK ja surm esinesid sagedamini prolongeeritud AB ravi grupis.** 122 patogeeni isoleeriti 100 positiivsest verekülvist: (82 grampos. bakterit, 30 gramneg. bakterit ja 10 candida) 76 lapsel. Patogeenid olid: *Candida, Citrobacter, Escherichia coli, Enterobacter, Enterococcus,* B-grupi streptokokk ja teised streptokokid, *Klebsiella, Pseudomonas, Serratia, Staphylococcus aureus,* koagulaas-negatiivne *Staphylococcus* (isoleeriti ka 1/3 hilise sepsise juhtudel). **Tulemused: prolongeeritud empiiriline antibakteriaalne ravi oli seotud 2 korda kõrgema hilise sepsise esinemissagedusega, NEK-i või surmaga ja 3 korda kõrgem hilise sepsise esinemissagedusega eraldi. Soovitav on kiire AB ravi lõpetamine, kui külvid on negatiivsed ja kliiniline leid ning laboratoorsed tulemused näitavad madalat sepsise riski.** **<u>Järeldused:</u> prolongeeritud empiirilised i/v antibiootikumid steriilsete külvidega enneaegsetele vastsündinutele esimesel elunädalal on seotud hilisemate tõsiste tulemustega.** Edaspidi tuleb uurida mõistlikku antibiootikumide kasutamise piirangut kui strateegiat, mis vähendab enneaegsetel vastsündinutel tõsiseid haigusi.	Pediatr. **2011** November ; 159(5): 720–725.
2010a. randomiseeritud kontrolluuring enneaegsete vastsündinutega, et võrrelda rutiinse antibakteriaalse ravi tulemusi sepsise esinemissagedusega. Esmane tulemus oli kliinilise sepsise esinemissagedus, sekundaarne tulemus positiivsete verekülvide, NEK-i II ja III staadiumi esinemissagedus või surm ja haiglasoleku kestus. Uuringusse kaasati 140 enneaegset, N=69, kontrollgrupp N=71. Sepsise esinemissagedus oli võrreldav mõlemas grupis: AB ravi saanute grupis oli 31,9% ja kontrollgupis 25.4%, P ¼ 0.392. Suremus oli võrdne mõlemas grupis. Kontrollgrupis oli märkimisväärselt rohkem positiivseid verekülve (P ¼ 0.002). NEK-i esinemissagedus ja haiglasoleku kestus olid võrreldavad mõlemas grupis. **Madala riskigrupiga enneaegsete grupis me ei leidnud tõendeid, et rutiinne antibakteriaalne ravi oli kaitsva efektiga või kasulik.**	**14.Routine antibiotic use in preterm neonates: a randomised controlled trial** A. Tagare, S. Kadam, U. Vaidya, A. Pandit Journal of Hospital Infection **(2010)** 74, 332e336
Ei ole võrdlusandmeid empiiriliselt kasutatavate erinevate antibiootikumide mõjust varasele soole kolonistasioonile samuti kliinilisele tõhususele eriti väikestel enneaegsetel <1000g vastsündinutel, kellel on risk varase algusega sepsisele. Ampitsiliin ja penitsilliin G kombinatsioonis gentamütsiiniga on kõige sagedamini soovitatud ja kasutatavad antibiootikumid neonataalse varase algusega sepsise empiirilises ravis (Mtitimila et al 2004, Tessin et al 1991). **Kaks ravimikombinatsiooni erinevad antibakteriaalse toime poolest, ampitsiliinil suurem efektiivsus gramnegatiivsetele mikroorganismidele nagu nagu *Escherichia coli.* Eristamine on tõenäoliselt kõige olulisem ELBW vastsündinute ravis, kuna**	**15.Ampicillin versus penicillin in the empiric therapy of extremely low-birthweight neonates at risk of early onset sepsis** Metsvaht T,Ilmoja M-L, Parm Ü,

gramnegatiivsed patogeenid, eriti *E. coli,* on uuringute alusel domineeriv varase algusega sepsist põhjustavate mikroorganismide populatsioonis (Ronnestad et al 2005, Klinger et al 2009, Lopez-Sastre et al 2000, Stoll et al 2005). **Meetodid**: Alagruppide analüüs teostati eriti väikestele enneaegstele, keda kaasati uuringusse 2-keskuselises uuringus, prospektiivses klastri-randomiseeritud uuringus, kus võrreldi ampitsilliini japenitsilliini kasutamist koos gentamütsiiniga esimesel 72 elutunnil. Esmast liitlõpptulemust (AB ravi ebaõnnestumine, kui oli vajalik muuta AB ravi 72 tunni jooksul ja /või surm 7 päeva jooksul), kolonisatsiooni kestustja sagedust opportunistlike aeroobsete mikroobidega hinnati kasutades hierarhilist mudelit, mis oli korrigeeritud uuringute perioodil uuringute keskustes. **Tulemused:** ampitsilliini (*n*=36) ja penitsilliini (*n*=39) grupis antibiootikumide muutmine, 7 päeva suremus ja liitlõpptulemused olid sarnase sagedusega. Neonataalne intensiivravi osakonna suremus enneaegsetel gestatsioonivanuses alla 26 nädala oli madalam ampitsilliin ravi saanute grupis. Ampitsiliin ravi oli seotud kõrgema *Klebsiella pneumonia* kolonisatsiooniga, sisaldades ampitsilliin-resistentseid tüvesid. **<u>Järeldus:</u> Esialgsed andmed viitavad kiireloomuliste andmete vajadusele, adekvaatselt võimsate uuringutega, varase antibiootikumidega ravi kohta, eriti väikeste enneaegsete alapopulatsioonides, kellel on risk varase algusega sepsiseks.**	Merila M, Maipuu L, Müürsepp P, Julge K,Sepp E, Lutsar I. Pediatrics International**(2011)** 53, 873–880
Kuigi ei ole hinnatud piisavalt tugevates kliinilistes uuringutes, aminoglükosiidi ja ampitsiliini või penitsiliini kombinatsioon on jäänud varase algusega sepsise ravi valikuks paljudes maailma osakondades (Mtitimila et al 2004, Clark et al 2006). Hiljutised muutused varase algusega sepsise bakteriaalses etioloogias, vähenenud B-grupi streptokoki (GBS) esinemissagedusega ja suurenenud *E.coli* esinemisega, tõstatas probleemi kahe raviskeemi potentsiaalsetes erinevusetes. Gramnegatiivsete patogeenide ülekaal varase algusega sepsise korral enneaegsetel vastsündinutel, raporteeritud Euroopas (Ronnestadet al 2005) ja Ameerika Ühendriikides (Stoll et al 2005, Bizzarro et al 2008), ja ka Iisraelis (Klinger et al 2009), soovitab kõrgema potentsiaalse efektiivsusega ampitsiliini vähemalt selles alapopulatsioonis. **Uuringu** (open label cluster randomized equivalence study) **eesmärgiks oli võrrelda ravi ampitsilliini (AMP) vs. penitsilliiniga (PEN) varase sepsise riskiga vastsündinutel, n=283, vastsündinud gestatsioonivanuses <28, <26GN ja >36GN.** Uuring tehti 2-s Eesti vastsündinute intensiivravi osakonnas, uuringusse olid kaasatud vastsündinud, kahtlusega varase algusega sepsisele, kelle vanus oli alla <72 tunni. Primaarne lõpptulemus oli kliiniline ebaõnnestumise sagedus väljendatuna antibiootikumi muutmise vajadusena 72 tunni jooksul ja/või 7 päeva üldsuremus. Soole kolonistasiooni jälgiti külvides võetuna perineaalpiirkonnast. **Tulemused: Tõestatud varase algusega sepsise esinemissagedus oli 4.9%.AMP** AMP (n = 142) või PEN (n = 141) **saanud vastsündinute hulgasantibiootikumi muutus 72 tunni jooksul**(10／142 vs. 10／141;	**16.Comparison of ampicillin plus gentamicin vs. penicillin plus gentamicin in empiric treatment of neonates at risk of early onset sepsis** Metsvaht T, Ilmoja M-L, Parm Ü, Maipuu L, Merila M, Lutsar I Acta Pædiatrica **2010,** 99, pp. 665–672

OR 1.02; 95% CI 0.40–2.59), **7 päeva suremus** (11⁄142 vs. 14⁄141; OR 0.76; 95% CI 0.33–1.75) **ja üldine ravi ebaõnnestumine** (20⁄142 vs. 20⁄141; OR 1.01; 95% CI 0.52–1.97) **esines sama sagedusega**. **Ainuke erinevus esines soole kolonisatsioonis:** madalam oli enterokokkidega, S. Aureusega ja AMP resistentse Acinetobacter spp. patsientide arv AMP grupis ja madalam S. haemolyticuse ja S. hominisega PEN grupis. **<u>Järeldus:</u> AMP ja PEN kombineerituna gentamütsiiniga omab sarnast efektiivsust varase algusega vastsündinu sepsise empiirilises ravis.**	

Kokkuvõtteks: Esmase antibakteriaalse ravi valikuna soovitatakse kasutada penitsilliini (bensüülpenitsilliini või ampitsilliini) koos gentamütsiiniga, kui kohalik mikrobioloogiline seire ei ole tuvastanud resistentsust, mille alusel võiks vajalikuks osutuda muu antibiootikumide kombinatsiooni kasutamine.

Empiirilise antibakteriaalse ravi annused (NEOFAX®)

Penitsilliin G: 25 000–50 000 TÜ/kg/dosi, veenisisene infusioon 15 min jooksul

Meningiidi korral kahekordista annust.

Postmenstruaalvanus (nädalaid)	Postnataalne vanus (päevi)	Doos (TÜ/kg/dosi)	Manustamise intervall (tundi)
≤29	0–28	25 000–50 000	12
30–36	0–14	25 000–50 000	12
37–44	0–7	25 000–50 000	12
>44	kõik	25 000–50 000	12

Ampitsilliin: 25–50 mg/kg/dosi, veenisiseselt aeglselt

Postmenstruaalvanus (nädalaid)	Postnataalne vanus (päevi)	Doos (mg/kg/dosi)	Manustamise intervall (tundi)
≤29	0–28	25–50	12
30–36	0–14	25–50	12
37–44	0–7	25–50	12
>44	kõik	25–50	12

Gentamütsiin: veenisisene infusioon perfuusoriga 30 min jooksul

Postmenstruaalvanus (nädalaid)	Postnataalne vanus (päevi)	Doos (mg/kg/dosi)	Manustamise intervall (tundi)
≤29	0–7	5	48
30–34	0–7	4,5	36
≥35	kõik	4	24

Viited
Ravijuhendid

1. Antibiotics for early-onset neonatal infection: antibiotics for the prevention and treatment of early-onset neonatal infection

National Collaborating Centre for Women's and Children's Health Commissioned by the National Institute for Health and Clinical Excellence - **(NICE) August 2012.** Published by the Royal College of Obstetricians and Gynaecologists (RCOG).

-Evidence Update June 2014.

Population-based surveillance in the UK, pp.38-41

Central to the management of early-onset neonatal infection is an awareness of the causativebacteria. The UK is fortunate to have population-based microbiological surveillance data, and two UKpopulation-based neonatal infection surveillance studies were published during the development ofthe guideline.

The first study (Muller-Pebody 2011) described bacteria isolated from neonatal blood cultures, andtheir susceptibilities to antibiotics commonly recommended for empirical treatment of suspectedinfection, using data from the Health Protection Agency's (HPA) LabBase2 database for the periodJanuary 2006 to March 2008. The database captures microbiological results submitted voluntarily by90% of laboratories in England and Wales. Table 2.1 summarises bacterial isolates associated withearly-onset neonatal infection (onset within 48 hours of birth).This table excludes *coagulase-negativestaphylococci* (CONS). In the context of early-onset neonatal infection CONS are usually regarded asblood sample contaminants (although true CONS infection can arise from hospital-acquired infection,most commonly as late-onset neonatal infection). The data reported in this study were acquired usingthe HPA's passive microbiological surveillance scheme, and so the clinical importance of the bacterialisolates cannot be established.

Table 2.1 Bacteria isolated from blood cultures from babies with early-onset neonatal infection (onset within 48 hours of birth) in England and Wales, January 2006 to March 2008[a]

Micro-organism	Number of isolates	Percentage of all isolates
Gram positive	**920**	**77**
Group B streptococcus	477	40
Non-pyogenic streptococci[b]	142	12
Staphylococcus aureus	75	6
Enterococcus species	49	4
Micrococcus species	35	3
Streptococcus pneumoniae	32	3
Diphtheroids	32	3
Beta-haemolytic streptococci	28	2
Listeria monocytogenes	13	1
Bacillus species	10	1
Group A streptococci	5	<1
Propionibacterium species	3	<1
Other[c]	19	2
Gram negative	**270**	**23**
Escherichia coli	137	12
Enterobacteriaceae[d]	35	3
Haemophilus influenzae	34	3
Pseudomonas species	18	2
Acinetobacter species	12	1
Haemophilus parainfluenzae	8	1
Haemophilus species	4	<1
Other[e]	22	2
Total	**1190**	**100**

[a] Source: Muller-Pebody 2011; excludes coagulase-negative staphylococci (a Gram-positive micro-organism), for which there were 326 isolates in the same population and time period

[b] *Streptococci viridans, S mitis, S oralis, S salivarius, S sanguinis* group, *S intermedius, S milleri, S anginosus, S acidominimus, S gordonii, Abiotrophia* species, *Aerococcus* species

[c] *Streptococcus* group G, *Streptococcus* group C, *Streptococcus* group D, *Bacillus* other named, *Bacteroides* species, *Lactococcus cremoris, Listeria* species, *Eubacterium* species, *Gardnerella vaginalis, S anaerobic,S dysgalactiae, S equisimilis*

[d] *Klebsiella* species, coliform, *Enterobacter* species, *Morganella* species, *Kluyvera* species, *Citrobacter* species, *Pantoea* species, *Proteus* species, *Salmonella paratyphi, Serratia*species

[e] *Moraxella* species, *Stenotrophomonas maltophilia, Bacteroides* species, *Neisseria* species, *Sphingomonas paucimobilis, Aeromonas* species, *Peptostreptococcus* species, *Burkholderia cepaci, Oligella urethralis, Roseomonas* species, *Weeksella virosa*

The second study (Vergnano 2011) provided a description of NeonIN, a network of level 2 and level 3neonatal units in England involved in the prospective collection of clinical and microbiological data onepisodes of neonatal infection. The study included a report on micro-organisms isolated from blood,cerebrospinal fluid (CSF) and urine samples in babies with early- or late-onset neonatal infection(although all urine infections reported were late-onset)and who received antibiotics for at least 5 days;antibiotic susceptibilities of the reported organisms were also reported. The report was compiled frominformation in the NeonIN database for the 3year period from 1 January 2006 to 31 December 2008,at the end of which 12 neonatal units (two level 2 and 10 level 3) were active participants.

Table 2.2 summarises bacterial isolates associated with each episode of early-onset neonatalinfection (onset of infection less than 48 hours after birth), excluding CONS, which were not recordedfor the entire study period, and fungal pathogens (*Candida albicans*). The data reported in this studywere acquired from neonatal units with an interest in neonatal infection and so they are expected tohave a different case mix from other centres (for example more babies in these units undergosurgery).

Table 2.2 Bacteria isolated from blood or cerebrospinal fluid cultures from babies with early-onset neonatal infection (onset within 48 hours of birth) in a network of level 2 and level 3 neonatal units in England, January 2006 to December 2008[a]

Micro-organism	Number of episodes	Percentage of all episodes
Gram positive	**94**	**76**
Group B streptococcus	65	52
Non-pyogenic streptococci[b]	5	4
Staphylococcus aureus	6	5
Enterococcus species	3	2
Micrococcus species	1	<1
Streptococcus pneumoniae	2	2
Diphtheroids	1	<1
Beta-haemolytic streptococci	0	0
Listeria monocytogenes	7	6
Bacillus species	4	3
Group A streptococci	0	0
Propionibacterium species	0	0
Other[c]	0	0
Gram negative	**30**	**24**
Escherichia coli	23	19
Enterobacteriaceae[d]	2	2
Haemophilus influenzae	4	3
Pseudomonas species	1	<1
Acinetobacter species	0	0
Haemophilus parainfluenzae	0	0
Haemophilus species	0	0
Other[e]	0	0

Total	**124**	**100**

[a] Source: Vergnano 2011; excludes coagulase-negative staphylococci (a Gram positive micro-organism), for which the number of episodes in the same population and time period was not reported, and fungal pathogens (one episode was associated with *Candida albicans*)

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Introduction

[b] *Streptococci viridans*, *S miti*, alpha-haemolytic streptococci, other Streptococcus species
[c] *Streptococcus* group G, *Streptococcus* group C, *Streptococcus* group D, *Bacillus* other named, *Bacteroides* species, *Lactococcus cremoris*, *Listeria* species, *Eubacterium* species, *Gardnerella vaginalis*, *S anaerobic*, *S dysgalactiae*, *S equisimilis*
[d] *Morganella* species, *Serratia* spp
[e] *Neisseria* species

Despite the differences in case mix, the two studies reported similar proportions of isolates orepisodes of early-onset neonatal infection being caused by Gram-positive bacteria other than CONSand Gram-negative bacteria (about 75% and 25%, respectively). In both studies the most frequentcausative Gram-positive and Gram-negative bacteria for early-onset neonatal infection were*Streptococcus agalactiae* (group B streptococcus; GBS) and *Escherichia coli*, respectively. However,*Listeria monocytogenes* accounted for 1% of documented infections in the first study (Muller-Pebody2011) compared with 6% in the second study (Vergnano 2011).The first study reported that 97% of all causative bacteria other than CONS for early-onset neonatalinfection were susceptible to an antibiotic regimen combining benzylpenicillin with gentamicin, 99%were susceptible to amoxicillin combined with benzylpenicillin, 96% were susceptible to cefotaxime asmonotherapy and 100% were susceptible to amoxicillin combined with cefotaxime. Thesusceptibilities of GBS and *E.coli* to each of these regimens were in the range 98–100%. However, theproportions of isolates that were tested for susceptibility to the various antibiotic regimens variedconsiderably (47%, 67%, 16% and 49%, respectively), perhaps because certain isolates were notexpected to be susceptible to particular antibiotic regimens. The authors recommended the use ofgentamicin-based antibiotic regimens over cefotaxime-based regimens in neonatal units because thefrequent use of third-generation cephalosporins, such as cefotaxime, has been linked to increasedincidence of resistant bacterial pathogens in these settings.The second study (Vergnano 2011) reported that 95% of bacterial pathogens other than CONS thatcause early-onset neonatal infection were susceptible to an antibiotic regimen combiningbenzylpenicillin with gentamicin. Susceptibility to antibiotic regimens varies between bacterialorganisms, and in this study all isolates of *Staphylococcus aureus* were reported to be resistant to theregimen combining benzylpenicillin and gentamicin. The authors of this study concluded that theNeonIN data did not support the use of an antibiotic regimen combining ampicillin and cefotaxime forempirical treatment of early-onset neonatal infection because it provided lower coverage for themajority of causative organisms and its use encourages the development of antibiotic resistance.The UK population-based surveillance studies demonstrate that surveillance systems are useful, butthey need to be improved. Collaborations between networks such as NeonIN and the HPA will becentral to improving the management of early-onset neonatal infection. The GDG recommendedfurther research in this area (see Chapter 9). pp. 38-41

Investigations before starting antibiotics in the baby p.185

Evidence statements

Identifying asymptomatic babies who should receive antibiotictreatment

A low peripheral WBC count (4.99×103/microlitre or less) is a very useful test for ruling in early-onset neonatal infection in asymptomatic at-risk babies at 1 hour or more after birth, but it is not a useful test at less than 1 hour after birth(low quality evidence).

A low absolute neutrophil count (0.99×103/microlitre or less) is a moderately useful test for ruling in early-onset neonatal infection in asymptomatic at-risk babies at less than 1 hour after birth and a very useful test at 1 hour or more after birth (low quality evidence). A moderately low absolute neutrophil count (1–1.99×103/microlitre) is a very useful test for ruling in early-onset neonatal infection in asymptomatic at-risk babies at 4 hours or more after birth, but it is not a useful test at less than 4 hours after birth (low quality evidence).

An I:T ratio of 0.6 or more is a moderately useful test for ruling in early-onset neonatal infection in asymptomatic at-risk babies at less than 4 hours after birth, and a very useful test at 4 hours or more after birth(low quality evidence).

No evidence was identified relating to the accuracy of tests based on peripheral WBC counts forruling out early-onset neonatal infection. A composite measure of abnormal WBC count (defined as total WBC count 5000/mm3 or less or 30,000/mm3 or more, or absolute neutrophil count less than 1500 mm3, or immature:mature neutrophil ratio more than 0.2) is not a useful test for ruling in or ruling out early-onset neonatal infection in asymptomatic at-risk babies (low quality evidence). No evidence was identified relating to tests based on CRP, procalcitonin, platelet count, surface swabs (including eye swabs and umbilical cord swabs), gastric aspirates or urine microscopy or culture.

Babies about to start antibiotic treatment

CRPat presentation is, at best, a very useful test for ruling in early-onset neonatal infection,particularly when serial testing is performed over a period of 2 days following presentation, but it is not a useful test for ruling out early-onset neonatal infection.In some studies, CRP at presentation was not a useful test for ruling in or ruling out early-onset neonatal infection (moderate to high quality evidence).

Procalcitonin at presentation is, at best, a moderately useful test for ruling in early-onset neonatal infection but it is not a useful test for ruling out early-onset neonatal infection. In most studies, procalcitonin at presentation was not a useful test for ruling in or ruling out early-onset neonatal infection (low to moderate quality evidence).

Interleukins 6, 8 and 10 at presentation are not useful tests for ruling in early-onset neonatal infection but, at best, interleukin 8 is a moderately useful test for ruling out early-onset neonatal infection. In most studies, interleukins 6, 8 and 10 at presentation were not useful tests for ruling in or ruling out early-onset neonatal infection (low to high quality evidence).

A low peripheral WBC count (6000 cells/mm3 or less) at presentation is, at best, a moderately useful test for ruling in early-onset neonatal infection but it is not a useful test for ruling out early-onset neonatal infection (low to moderate quality evidence).

A high peripheral WBC count (25,000 cells/mm3 or more) at presentation is not a useful test for ruling in or ruling out early-onset neonatal infection (low quality evidence).

A low peripheral neutrophil count (4000 cells/mm3 or less) at presentation is not a useful test for ruling in or ruling out early-onset neonatal infection (low quality evidence).

An I:T ratio of 0.2 or more at presentation is not a useful test for ruling in early-onset neonatalinfection but it is, at best, a moderately useful test for ruling out early-onset neonatal infection (low to high quality evidence).

Platelet count at presentation is not a useful test for ruling in or ruling out early-onset neonatalinfection (low quality evidence).

PCR at presentation is, at best, a very useful test for ruling in early-onset neonatal infection and ruling out early-onset neonatal infection (low quality evidence). In most studies, PCR at presentation was a moderately useful test for ruling in early-onset neonatal infection but it was not a useful test for ruling out early-onset neonatal infection (moderate quality evidence).

Composite measures at presentation based on CRP and either interleukins or I:T ratio are not useful for ruling in early-onset neonatal infection but are, at best, moderately useful for ruling out early-onset neonatal infection. In some studies, composite measures at presentation based on CRP and either interleukins or I:T ratio were not useful tests for ruling in or ruling out early-onset neonatal infection (moderate to high quality evidence).

Composite measures at presentation based on procalcitonin and either interleukins or I:T ratio are not useful tests for ruling in early-onset neonatal infection but are, at best at best, moderately useful tests for ruling out early-onset neonatal infection (low quality evidence).

Composite measures at presentation based on WBC count, CRP, I:M ratio and I:T ratio are not useful tests for ruling in early-onset neonatal infection but are, at best at best, moderately useful tests for ruling out early-onset neonatal infection (very low quality evidence).

A composite measure at presentation based on maternal and neonatal clinical factors and interleukins is, at best, a moderately useful test for ruling in early-onset neonatal infection and a very useful test for ruling out early-onset neonatal infection (low quality evidence).

Surface swabs (from the skin, ear, nose or pharynx) are, at best, very useful tests for ruling in and ruling out systemic early-onset neonatal infection. In some studies, surface swabs were not useful tests for ruling in or ruling out early-onset neonatal infection (moderate quality evidence).

Urine latex agglutination testing for GBS antigen is, at best, a very useful test for ruling in and ruling out early-onset neonatal infection. In some studies, urine latex agglutination testing for GBS antigen was not a useful test for ruling in or ruling out early-onset neonatal infection (low to moderate quality evidence). Urine culture is a very useful test for ruling in early-onset neonatal infection, but it is not a useful test for ruling out early-onset neonatal infection (low quality evidence).

CSF parameters (one or more of white cell count, protein concentration and glucose concentration) are, at best, very useful tests for ruling in early-onset neonatal infection and moderately useful tests for ruling out early-onset neonatal infection. In most studies, CSF parameters were not useful tests for ruling in or ruling out early-onset neonatal infection (very low quality evidence). Composite measures at presentation based on CSF parameters (one or more of white cell count, protein concentration and glucose concentration) and neonatal clinical factors are not useful tests to rule in bacterial meningitis but are, at best,

moderately useful tests to rule out bacterial meningitis. In some studies composite measures at presentation based on CSF parameters (one or more of white cell count, protein concentration and glucose concentration) and neonatal clinical factors were not useful tests for ruling in or ruling out bacterial meningitis (very low quality evidence).

No evidence was identified relating to tests based on cytokines, buffy coat examination, gastricaspirates or chest X-ray. No evidence specific to eye swabs and umbilical cord swabs was identified for inclusion.

Description of included studies(Antibiotics for suspected infection 197)

Fourteen studies reported in 15 articles were identified for inclusion for this review question (Agarwal 2002; de Alba Romero 1998; Hayani 1997; Isemann 1996; Itsarayoungyuen 1982; Langhendries 1993; Mercado 2004; Metsvaht 2007; Metsvaht 2010; Miall-Allen 1988; Muller 2007; Parm 2010; Rastogi 2002; Skopnik 1992; Snelling 1983).

Clinical outcomes reported in randomised controlled trials

Four RCTs compared the effectiveness of different antibiotics (or combinations of antibiotics) inbabies with suspected early-onset neonatal infection:

• One study reported in two articles evaluated the effectiveness of benzylpenicillin plusgentamicin compared to ampicillin plus gentamicin (Metsvaht 2010; Parm 2010).

• One study evaluated the effectiveness of benzylpenicillin plus gentamicin comparedwith ceftazidime (Snelling 1983).

• One study evaluated the effectiveness of gentamicin compared with tobramycin(Itsarayoungyuen 1982).

• One study evaluated the effectiveness of ticarcillin plus clavulanic acid compared withpiperacillin (with or without gentamicin; Miall-Allen 1988).

Seven RCTs evaluated clinical outcomes for different gentamicin dosing regimens in babies with

suspected early-onset neonatal infection:

• Four studies evaluated the effectiveness of gentamicin given every 24 hours(4–5 mg/kg/dose) compared with gentamicin given every 12 hours (2–3 mg/kg/dose); babies in both treatment arms also received ampicillin. **One study focused on near-termand term babies (birthweight 2500 g or more)** with suspected infection in the first 7 daysof life (ampicillin dosing schedule not reported; Agarwal 2002). Another study focusedon full-term babies with suspected infection in the first 3 days of life (ampicillin dosage200 mg/kg/day; Skopnik 1992). Another study focused **on near-term and term babies(gestational age 34 weeks or more, birthweight 2000 g or more)** with suspected infectionin the first 24 hours of life (ampicillin dosage regimen not reported; Hayani 1997); theremaining study focused on babies with suspected early-onset neonatal infection(ampicillin dosage regimen not reported; de Alba Romero 1998).

• Two studies evaluated the effectiveness of gentamicin given every 48 hours (4.5–5 mg/kg/dose) compared with gentamicin given every 18–24 hours (2.5–3 mg/kg/dose); babies in both treatment arms also received ampicillin (ampicillin dosing schedules not reported). One study **focused specifically on very low birthweight babies (600–1500 g) with suspected neonatal infection in the first 7 days of life** (Rastogi 2002) and **the other focused specifically on preterm** babies (less than 34 weeks of gestation, birthweight 750–2000 g) with suspected neonatal infection in the first 24 hours of life (Mercado 2004).

• One study evaluated the effectiveness of a loading dose of gentamicin (4 mg/kg) compared with the standard initial dose of gentamicin (2.5 mg/kg) in babies with suspected neonatal infection in the first 12 hours of life; babies in both treatment arms received maintenance doses of gentamicin (2.5 mg/kg every 12, 18 or 24 hours depending on gestational age and birthweight) and ampicillin (200–400 mg/kg/day; Isemann 1996).

Six of the studies that reported clinical outcomes associated with gentamicin treatment includedtherapeutic drug monitoring and individualised dosage adjustment for gentamicin based on thresholds for peak and trough serum gentamicin concentrations, serum creatinine concentrations and urine output (Agarwal 2002; de Alba Romero 1998; Hayani 1997; Isemann 1996; Rastogi 2002; Snelling 1983), but details of the calculations used to determine adjusted dosages were not reported. In the remaining studies involving gentamicin treatment, therapeutic drug monitoring and dosage adjustment for gentamicin was not reported in either treatment arm. Studies that evaluate the effectiveness of strategies for therapeutic drug monitoring and individualised dosage adjustment for gentamicin are discussed in a separate review question (see Chapter 11).

One study evaluated the effectiveness of amikacin given every 24 hours (15 mg/kg/dose) in near-term and term babies (34 weeks or more of gestation) with suspected early-onset neonatal infection compared with amikacin given every 12 hours (7.5 mg/kg/dose); babies in both treatment arms also received ampicillin every 12 hours (Langhendries 1993).

Pharmacokinetic and pharmacodynamic studies

Based on the **GDG's – Guideline Development Group** initial consideration of clinical outcomes reported in RCTs, the pharmacokinetics and pharmacodynamics of benzylpenicillin and gentamicin were prioritised for evaluation. All seven RCTs that evaluated clinical outcomes for different gentamicin dosing regimens also reported pharmacokinetic outcomes. No further RCTs reporting pharmacokinetic outcomes associated with gentamicin treatment were identified for inclusion.

No RCTs reporting pharmacokinetic or pharmacodynamic outcomes associated with benzylpenicillin treatment were identified for inclusion, but two studies of other designs were identified for inclusion:

• One **non-randomised comparative study evaluated the pharmacokinetics of two doses of intravenous benzylpenicillin (25,000 IU/kg every 12 hours and 50,000 IU/kg every 12 hours) invery preterm babies (less than 28 weeks of gestation, birthweight less than 1200 g)** with suspected infection in the first 3 days of life; babies in both treatment arms also received gentamicin (5 mg/kg every 48 hours; Metsvaht 2007).

• The other study used Monte Carlo simulation to evaluate the **pharmacokinetics of intravenous benzylpenicillin (50,000 IU/kg every 12 hours) in preterm babies (less than 32 weeks' gestation)** with suspected infection in the first 3 days of life; babies in both treatment arms also received tobramycin or cefotaxime (dosage regimens not reported; Muller 2007).

Evidence profiles

The evidence profiles for this review question are presented in Tables 9.1 to 9.14. Tables 9.1 to 9.4 contain evidence relating to comparisons between different antibiotics (or combinations of antibiotics). Tables 9.5 to 9.11 contain evidence relating to comparisons between different gentamicin dosing regimens, including pharmacokinetic outcomes. Table 9.12 contains evidence relating to comparisons between different amikacin dosing

regimens. Tables 9.13 and 9.14 contain evidence relating to the pharmacokinetics of benzylpenicillin.

Table 9.1 Evidence profile for ampicillin plus gentamicin compared with benzylpenicillin plus gentamicin in babies with suspected early-onset neonatal infection[a]

Number of studies	Number of babies		Effect		Quality
	Ampicillin plus gentamicin	Benzylpenicillin plus gentamicin	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Treatment failure (need for change of antibiotics or death within 7 days)					
1 (Metsvaht 2010)	20/142 (14.1%)	20/141 (14.2%)	RR 0.99 (0.56 to 1.76)*	1 more per 1000 (62 fewer to 108 more)*	Low
Mortality					
7-day mortality					
1 (Metsvaht 2010)	11/142 (7.7%)	14/141 (9.9%)	RR 0.78 (0.37 to 1.66)*	22 fewer per 1000 (63 fewer to 66 more)*	Low
Mortality in the neonatal intensive care unit					
1 (Metsvaht 2010)	13/142 (9.2%)	23/141 (16.3%)	RR 0.56 (0.30 to 1.06)*	72 fewer per 1000 (114 fewer to 10 more)*	Low

Number of studies	Number of babies		Effect		Quality
	Ampicillin plus gentamicin	Benzylpenicillin plus gentamicin	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Mortality in the neonatal intensive care unit in babies < 26 weeks' gestation[b]					
1 (Metsvaht 2010)	6/24 (25.0%)	13/21 (61.9%)	RR 0.40 (0.19 to 0.87)*	371 fewer per 1000 (80 fewer to 501 fewer)*	Low
Colonisation with ampicillin-resistant Gram-negative bacteria					
1 (Metsvaht 2010)	44/142 (30.9%)	44/141 (31.2%)	RR 0.99 (0.70 to 1.40)*	3 fewer per 1000 (94 fewer to 125 more)*	Low
Colonisation with *Staphylococcus haemolyticus*°					
Number of babies colonised					
1 (Parm 2010)	NR/139	NR/137	NC	More in the ampicillin group *P* = 0.039	Low
Mean colonisation duration (days colonised per 100 intensive care unit days)[d]					
1 (Parm 2010)	NR	NR	NC	Longer in the ampicillin group *P* = 0.001	Low
Colonisation with *Klebsiella pneumoniae*°					
Number of babies colonised					
1 (Parm 2010)	NR/139	NR/137	NC	More in the ampicillin group *P* = 0.107	Low
Mean colonisation duration (days colonised per 100 intensive care unit days)[d]					
1 (Parm 2010)	NR	NR	NC	Longer in the ampicillin group *P* = 0.012	Low
Colonisation with *Staphylococcus hominis*°					
Number of babies colonised					
1 (Parm 2010)	NR/139	NR/137	NC	More in the ampicillin group *P* = 0.003	Low
Mean colonisation duration (days colonised per 100 intensive care unit days)[d]					
1 (Parm 2010)	NR	NR	NC	Longer in the ampicillin group *P* = 0.001	Low
Colonisation with *Enterococcus* species°					
Number of babies colonised					
1 (Parm 2010)	NR/139	NR/137	NC	Fewer in the ampicillin group *P* < 0.001	Low

Number of studies	Number of babies		Effect		Quality
	Ampicillin plus gentamicin	Benzylpenicillin plus gentamicin	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Mean colonisation duration (days colonised per 100 intensive care unit days)[d]					
1 (Parm 2010)	NR	NR	NC	Shorter in the ampicillin group *P* = 0.001	Low
Colonisation with *Staphylococcus aureus*[e]					
Number of babies colonised					
1 (Parm 2010)	NR/139	NR/137	NC	Fewer in the ampicillin group *P* = 0.006	Low
Mean colonisation duration (days colonised per 100 intensive care unit days)[d]					
1 (Parm 2010)	NR	NR	NC	Shorter in the ampicillin group *P* = 0.052	Low
Colonisation with ampicillin-resistant *Acinetobacter* species[e]					
Number of babies colonised					
1 (Parm 2010)	NR/139	NR/137	NC	Fewer in the ampicillin group *P* = 0.996	Low
Mean colonisation duration (days colonised per 100 intensive care unit days)[d]					
1 (Parm 2010)	NR	NR	NC	Shorter in the ampicillin group *P* = 0.001	Low
Number of babies colonised with *Acinetobacter species*[e]					
1 (Parm 2010)	NR/139	NR/137	NC	Fewer in the ampicillin group *P* = 0.224	Low
Number of babies colonised with *Enterobacter cloacae*[e]					
1 (Parm 2010)	NR/139	NR/137	NC	Fewer in the ampicillin group *P* = 0.142	Low

NC not calculable, NR not reported, P probability, RR relative risk

* Calculated by the NCC-WCH technical team from data reported in the article

[a] Early-onset infection defined as infection in the first 72 hours of life

[b] Mortality in other groups classified by gestational age (< 28 weeks and > 36 weeks) not reported; possibility of selective reporting of statistically significant results

[c] Results of multivariate mixed effect model analysis

[d] Monitoring for colonisation was conducted via rectal swabs on admission to the intensive care unit and twice a week thereafter until discharge from the unit or day 60 if this occurred earlier; colonisation duration represents the ratio of colonising days to 100 intensive care unit days counted from the first to last positive culture with 2 days added to compensate for the sampling interval of 3–4 days

Table 9.2 Evidence profile for ceftazidime compared with benzylpenicillin plus gentamicin in babies with suspected early-onset neonatal infection[a]

Number of studies	Number of babies		Effect		Quality
	Ceftazidime	Gentamicin plus benzylpenicillin	Relative (95% confidence interval)	Absolute (95% confidence interval)	
1 (Snelling 1983)	31/31 (100%)	24/24 (100%)	RR 1.00 (0.93 to 1.07)*	0 fewer per 1000 (70 fewer to 70 more)*	Low

RR relative risk

* Calculated by the NCC-WCH technical team from data reported in the article

[a] Early-onset infection defined as infection in the first 48 hours of life

Table 9.3 Evidence profile for tobramycin compared with gentamicin in babies with suspected early-onset neonatal infection[a]

Number of studies	Number of babies		Effect		Quality
	Tobramycin	Gentamicin	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Kidney damage[b] (nephrotoxicity)					
1 (Itsarayoungyuen 1982)	4/30 (13%)	3/20 (15%)	RR 0.89 (0.22 to 3.55)*	17 fewer per 1000 (117 fewer to 383 more)*	Low
Hearing damage[c] (ototoxicity)					
1 (Itsarayoungyuen 1982)	0/30 (0%)	0/20 (0%)	NC	NC	Low

FENa fractional excretion of sodium, NAG N-acetyl glucosamine, NC not calculable, RR relative risk, U:S urine to serum

* Calculated by the NCC-WCH technical team from data reported in the article

[a] Early-onset infection defined as infection in the first 72 hours of life

[b] Babies who had an increase in serum creatinine of ≥0.4 mg% and developed renal abnormalities (such as haematuria, proteinuria, granular casts, decrease in U:S creatinine ratio, increase in NAG enzyme and increase in FENa) were considered to have developed nephrotoxicity. Assessments were made every 3 days during treatment and when treatment was stopped. 4/20 (20%) babies who received gentamicin and 8/30 (27%) babies who received tobramycin also received concurrent treatment with potentially nephrotoxic medications (for example methicillin, furosemide or indomethacin). No baby was suspected to have any renal abnormalities at the time of inclusion to the study. All seven babies who developed nephrotoxicity were judged to be premature and as having hyaline membrane disease

[c] Auditory function was measured by behavioural screening and/or auditory brainstem response. Timings and frequency of assessment was not described by authors

Table 9.5 Evidence profile for gentamicin given every 24 hours (4 mg/kg/dose) compared with gentamicin given every 12 hours (2.5 mg/kg/dose) in near-term and term babies (birthweight ≥ 2500 g) with suspected infection in the first 7 days of life; all babies also received ampicillin (dosage regimen not reported)

Number of studies	Number of babies		Effect		Quality
	Gentamicin every 24 hours (4 mg/kg/dose)	Gentamicin every 12 hours (2.5 mg/kg/dose)	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Neonatal adverse events					
Hearing impairment (assessed by a hearing screen test before discharge from hospital)					
1 (Agarwal 2002)	0/20 (0%)	0/21 (0%)	NC	NC	Low
Pharmacokinetics: measurements after the first dose					
Peak concentrations 6–12 microgram/ml after the first dose					
1 (Agarwal 2002)	16/20 (80%)	15/21 (71%)	RR 1.12 (0.79 to 1.59)*	86 more per 1000 (150 fewer to 421 more)*	Low
Peak concentrations 8–12 microgram/ml after the first dose					
1 (Agarwal 2002)	10*/20 (50%)	2*/21 (10%)	RR 5.25 (1.31 to 21.06)*	405 more per 1000 (30 more to 1000 more)*	Low

Number of studies	Number of babies		Effect		Quality
	Gentamicin every 24 hours (4 mg/kg/dose)	Gentamicin every 12 hours (2.5 mg/kg/dose)	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Pharmacokinetics: measurements at 24 hours					
Trough concentrations < 0.5 microgram/ml before the 24-hour dose					
1 (Agarwal 2002)	2/20 (10%)	0/21 (0%)	RR 5.24 (0.27 to 102.81)	NC	Low
Trough concentrations < 1 microgram/ml before the 24-hour dose					
1 (Agarwal 2002)	11/20 (55%)	2/21 (10%)	RR 5.78 (1.46 to 22.88)*	455 more per 1000 (44 more to 1000 more)*	Low
Trough concentrations ≥ 2 microgram/ml before the 24-hour dose					
1 (Agarwal 2002)	0/20 (0%)	9/21 (43%)	RR 0.06 (0.00 to 0.89)*	403 fewer per 1000 (47 fewer to 429 fewer)*	Low
Peak concentrations 6–12 microgram/ml after the 24-hour dose					
1 (Agarwal 2002)	20/20 (100%)	16/21 (76%)	RR 1.30 (1.01 to 1.67)*	229 more per 1000 (8 more to 510 more)*	Low
Peak concentrations 8–12 microgram/ml after the 24-hour dose					
1 (Agarwal 2002)	16/20 (80%)	6/21 (30%)	RR 2.80 (1.38 to 5.70)*	514 more per 1000 (109 more to 1000 more)*	Low
Peak concentrations > 12 microgram/ml after the 24-hour dose					
1 (Agarwal 2002)	0/20 (0%)	0/21 (0%)	NC	NC	Low
Pharmacokinetics: measurements at 48 hours					
Trough concentrations < 0.5 microgram/ml before the 48-hour dose					
1 (Agarwal 2002)	1/20 (5%)	0/21 (0%)	RR 3.14 (0.14 to 72.92)	NC	Low
Trough concentrations < 1 microgram/ml before the 48-hour dose					
1 (Agarwal 2002)	11/20 (55%)	3/21 (14%)	RR 3.85 (1.26 to 11.80)	407 more per 1000 (37 more to 1000 more)*	Low
Trough concentrations ≥ 2 microgram/ml before the 48-hour dose					
1 (Agarwal 2002)	0/20 (0%)	6/21 (29%)	RR 0.08 (0.00 to 1.34)	263 fewer per 1000 (286 fewer to 97 more)*	Low

Number of studies	Number of babies		Effect		Quality
	Gentamicin every 24 hours (4 mg/kg/dose)	Gentamicin every 12 hours (2.5 mg/kg/dose)	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Peak concentrations 6–12 microgram/ml after the 48-hour dose					
1 (Agarwal 2002)	19/19 (100%)	15/21 (71%)	RR 1.38 (1.05 to 1.83)*	271 more per 1000 (36 more to 593 more)*	Low
Peak concentrations 8–12 microgram/ml after the 48-hour dose					
1 (Agarwal 2002)	14*/19 (75%)	2*/21 (10%)	RR 7.74 (2.02 to 29.71)*	271 more per 1000 (36 more to 593 more)*	Low
Peak concentration > 12 microgram/ml after the 48-hour dose					
1 (Agarwal 2002)	0/20 (0%)	0/21 (0%)	NC	NC	Low
All peak concentrations over the 48-hour period					
Peak concentrations of 6–12 microgram/ml after the first, 24-hour and 48-hour doses					
1 (Agarwal 2002)	55/59 (93%)	36/63 (57%)	RR 1.63 (1.30 to 2.04)*	360 more per 1000 (171 more to 594 more)*	Low
Peak concentrations of 8–12 microgram/ml after the first, 24-hour and 48-hour doses					
1 (Agarwal 2002)	41*/59 (70%)	10*/63 (15%)	RR 4.38 (2.42 to 7.92)*	537 more per 1000 (225 more to 1000 more)*	Low

NC not calculable, RR relative risk

* Calculated by the NCC-WCH technical team from data reported in the article

Table 9.7 Evidence profile for gentamicin given every 24 hours (5 mg/kg/dose) compared with gentamicin given every 12 hours (2.5 mg/kg/dose) in near-term and term babies (gestational age ≥ 34 weeks, birthweight ≥ 2000 g) with suspected infection in the first 24 hours of life; all babies also received ampicillin (dosage regimen not reported)

Number of studies	Number of babies		Effect		Quality
	Gentamicin every 24 hours (5 mg/kg/ dose)	Gentamicin every 12 hours (2.5 mg/kg/ dose)	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Neonatal adverse events					
Kidney impairment (assessed by serum creatinine concentration and glomerular filtration rate)					
1 (Hayani 1997)	0/11 (0%)	0/15 (0%)	NC	NC	Low
Pharmacokinetics					
Trough concentrations > 2.0 microgram/ml before dose on the second or third day					
1 (Hayani 1997)	1/11 (9%)	6/15 (40%)	RR 0.23 (0.03 to 1.63)*	308 fewer per 1000 (388 fewer to 252 more)*	Low

NC not calculable, RR relative risk

* Calculated by the NCC-WCH technical team from data reported in the article

Table 9.8 Evidence profile for gentamicin given every 24 hours (5 mg/kg/dose) compared with gentamicin given every 12 hours (2.5 mg/kg/dose) in babies with suspected early-onset neonatal infection; all babies also received ampicillin (dosage regimen not reported)

Number of studies	Number of babies		Effect		Quality
	Gentamicin every 24 hours (5 mg/kg/ dose)	Gentamicin every 12 hours (2.5 mg/kg/ dose)	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Neonatal adverse events					
Kidney impairment (assessed by the N-acetyl-D-glucosaminidase:creatinine ratio)					
1 (de Alba Romero 1998)	0/33 (0%)	0/32 (0%)	NC	NC	Low
Pharmacokinetics					
Trough concentrations > 2.0 microgram/ml before dose on the fourth day of treatment					
1 (de Alba Romero 1998)	4*/33 (12%)	7*/32 (22%)	RR 0.55 (0.18 to 1.71)*	98 fewer per 1000 (179 fewer to 155 more)*	Low
Peak concentrations > 12.0 microgram/ml after dose on the fourth day of treatment					
1 (de Alba Romero1 998)	0/33 (0%)	1/32 (3%)	RR 0.32 (0.01 to 7.66)*	21 fewer per 1000 (31 fewer to 208 more)*	Low

NC not calculable, RR relative risk

* Calculated by the NCC-WCH technical team

Table 9.9 Evidence profile for gentamicin given every 48 hours (4.5–5 mg/kg/dose) compared with gentamicin given every 24 hours (2.5–3 mg/kg/dose) in very low birthweight babies (600–1500 g) with suspected neonatal infection in the first 7 days of life; all babies also received ampicillin (dosage regimen not reported)

Number of studies	Number of babies		Effect		Quality
	Gentamicin every 48 hours (4.5–5 mg/kg/ dose)	Gentamicin every 24 hours (2.5–3 mg/kg/ dose)	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Neonatal adverse events					
Hearing impairment (assessed by the brainstem-evoked auditory response test)					
1 (Rastogi 2002)	0/30 (0%)	0/28 (0%)	NC	NC	Low
Number of studies	**Number of babies**		**Effect**		**Quality**
	Gentamicin every 48 hours (4.5–5 mg/kg/ dose)	**Gentamicin every 24 hours (2.5–3 mg/kg/ dose)**	**Relative (95% confidence interval)**	**Absolute (95% confidence interval)**	
Kidney impairment (assessed by a reduction in urine output or an increase in serum creatinine ≥ 0.5 mg/dl)					
1 (Rastogi 2002)	0/30 (0%)	0/28 (0%)	NC	NC	Low
Pharmacokinetics: measurements after the first dose					
Peak concentrations < 5 microgram/ml after the first dose					
1 (Rastogi 2002)	0/29 (0%)	10/28 (36%)	RR 0.05 (0.00 to 0.75)*	339 fewer per 1000 (89 fewer to 357 fewer)*	Low
Peak concentrations of 6–12 microgram/ml after the first dose					
1 (Rastogi 2002)	27/29 (93%)	12/28 (43%)	RR 2.17 (1.40 to 3.37)*	501 more per 1000 (171 more to 1000 more)*	Low
Peak concentrations of 8–12 microgram/ml after the first dose					
1 (Rastogi 2002)	16*/29 (55%)	3*/28 (11%)	RR 5.15 (1.68 to 15.76)*	445 more per 1000 (73 more to 1000 more)*	Low
Peak concentrations >12 microgram/ml after the first dose					
1 (Rastogi 2002)	0/29 (0%)	1/28 (4%)	RR 0.32 (0.01 to 7.59)*	24 fewer per 1000 (35 fewer to 235 more)*	Low

Pharmacokinetics: measurements at 24 hours					
Trough concentrations < 2.0 microgram/ml at 24 hours					
1 (Rastogi 2002)	21/30 (70%)	NR[a]	NC	NC	Low
Trough concentrations < 1 microgram/ml at 24 hours					
1 (Rastogi 2002)	4/30 (13%)	NR[a]	NC	NC	Low
Peak concentrations < 5 microgram/ml after the 24-hour dose					
1 (Rastogi 2002)	-	5/28 (18%)	NC	NC	Low

Number of studies	**Number of babies**		**Effect**		**Quality**
	Gentamicin every 48 hours (4.5–5 mg/kg/ dose)	**Gentamicin every 24 hours (2.5–3 mg/kg/ dose)**	**Relative (95% confidence interval)**	**Absolute (95% confidence interval)**	
Pharmacokinetics: measurements at 48 hours					
Trough concentrations ≤ 0.5 microgram/ml before the 48-hour dose					
1 (Rastogi 2002)	9/30 (30%)	NR[b]	NC	NC	Low
Peak concentrations < 5 microgram/ml after the 48-hour dose					
1 (Rastogi 2002)	0/29 (0%)	5/28 (18%)	RR 0.09 (0.01 to 1.52)*	162 fewer per 1000 (177 fewer to 93 more)*	Low
Peak concentrations of 6–12 microgram/ml after the 48-hour dose					
1 (Rastogi 2002)	25/29 (86%)	19/28 (68%)	RR 1.27 (0.95 to 1.70)*	183 more per 1000 (34 fewer to 475 more)*	Low
Peak concentrations of 8–12 microgram/ml after the 48-hour dose					
1 (Rastogi 2002)	15*/29 (52%)	6*/28 (21%)	RR 2.41 (1.09 to 5.33)*	302 more per 1000 (19 more to 928 more)*	Low
Peak concentrations > 12 microgram/ml after the 48-hour dose					
1 (Rastogi 2002)	2/29 (7%)	0/28 (0%)	RR 4.83 (0.24, to 96.42)*	NC	Low
All peak concentrations over the 48-hour period					
Peak concentrations of 6–12 microgram/ml after the 24-hour and 48-hour doses					

1 (Rastogi 2002)	52/58 (90%)	31/56 (55%)	RR 1.62 (1.26 to 2.08)*	343 more per 1000 (144 more to 598 more)*	Low

NC not calculable, NR not reported, RR relative risk, SD standard deviation

* Calculated by the NCC-WCH technical team from data reported in the article

[a] Actual trough concentrations at 24 hours (mean ± SD, microgram/ml) 4.5–5.0 mg/kg once every 48 hour 1.72 ± 0.6 2.5; 3.0 mg/kg once every 24 hours 1.25±0.4 ($P = 0.0013$)

[b] Actual trough concentrations at 48 hours (mean ± SD, microgram/ml) 4.5–5.0 mg/kg once every 48 hour 0.70 ± 0.3 2.5; 3.0 mg/kg once every 24 hours 1.32 ± 0.4 ($P = 0.00001$)

Table 9.10 Evidence profile for gentamicin given every 48 hours (4.5–5 mg/kg/dose) compared with gentamicin given every 18–24 hours (2.5 mg/kg/dose) in preterm babies (< 34 weeks' gestation, birthweight 750–2000 g) with suspected neonatal infection in the first 24 hours of life; all babies also received ampicillin (dosage regimen not reported)

Number of studies	Number of babies		Effect		Quality
	Gentamicin every 48 hours (4.5–5 mg/kg/ dose)	Gentamicin every 18-24 hours (2.5 mg/kg/ dose)	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Neonatal adverse events					
Hearing impairment (assessed by the brainstem-evoked auditory response test)					
1 (Mercado 2004)	1/19 (5%)	2/21 (10%)	RR 0.55 (0.05 to 5.62)*	43 fewer per 1000 (90 fewer to 440 more)*	Low
Kidney impairment (assessed by a reduction in urine output < 1 ml/kg/hr or an increase in serum creatinine > 1 mg/dl)					
1 (Mercado 2004)	0/19 (0%)	0/21 (0%)	NC	NC	Low
Pharmacokinetics					
Trough concentrations > 2 microgram/ml after the second or third dose					
1 (Mercado 2004)	0/19 (0%)	1/21 (5%)	RR 0.37 (0.02 to 8.50)*	30 fewer per 1000 (47 fewer to 357 more)*	Low
Peak concentrations > 12 microgram/ml after the second or third dose					
1 (Mercado 2004)	2/19 (11%)	0/21 (0%)	RR 5.50 (0.28 to 107.78)*	NC	Low
Peak concentrations < 5 microgram/ml before the second or third dose					
1 (Mercado 2004)	0/19 (0%)	7/21 (33%)	RR 0.07 (0.00 to 1.20)*	310 fewer per 1000 (333 fewer to 67 more)*	Low

NC not calculable, RR relative risk

* Calculated by the NCC-WCH technical team from data reported in the article

Table 9.11 Evidence profile for a loading dose of gentamicin (4mg/kg) compared with a standard initial dose of gentamicin (2.5 mg/kg) in babies with suspected neonatal infection in the first 12 hours of life; all babies received maintenance doses of 2.5 mg/kg/dose every 12, 18 or 24 hours depending on gestational age and birthweight; all babies also received ampicillin (200–400 mg/kg/day)

Number of studies	Number of babies		Effect		Quality
	Gentamicin loading dose (4 mg/kg)	Gentamicin standard initial dose (2.5 mg/kg)	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Clinical effectiveness					
Mortality					
1 (Isemann 1996)	1/18 (6%)	0/16 (0%)	RR 2.68 (0.12 to 61.58)*	NC	Low
Hearing impairment (assessed by the brainstem-evoked auditory response test)					
1 (Isemann 1996)	3/12 (25%)	2/10 (20%)	RR 1.25 (0.26 to 6.07)*	50 more per 1000 (148 fewer to 1000 more)*	Low
Kidney impairment (assessed by decrease in urine output and increase in serum creatinine)					
1 (Isemann 1996)	1/18 (6%)	0/16 (0%)	RR 2.68 (0.12 to 61.58)*	NC	Low
Pharmacokinetics					
Peak concentrations (> 5 microgram/ml) after the first dose					
1 (Isemann 1996)	17/18 (94%)	1/16 (6%)	RR 15.11 (2.26 to 101.14)*	882 more per 1000 (79 more to 1000 more)*	Low
Peak concentrations > 10 microgram/ml after the first dose					
1 (Isemann 1996)	0/18 (0%)	0/16 (0%)	NC	NC	Low
Trough concentrations > 2 microgram/ml before the second dose (which was administered 12, 18 or 24 hours after the first dose, depending on gestational age and birthweight)					
1 (Isemann 1996)	10/18 (56%)	0/16 (0%)	RR 18.79 (1.19 to 297.03)*	NC	Low

NC not calculable, RR relative risk

* Calculated by the NCC-WCH technical team from data reported in the article

Table 9.12 Evidence profile for amikacin given every 24 hours (15 mg/kg/dose) compared with amikacin given every 12 hours (7.5 mg/kg/dose) in near-term and term babies (≥34 weeks' gestation) with suspected neonatal infection in the first 2 days of life; all babies also received ampicillin every 12 hours[a]

Number of studies	Number of babies		Effect		Quality
	Amikacin every 24 hours (15 mg/kg/ dose)	Amikacin every 12 hours (7.5 mg/kg/ dose)	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Cure rates for neonatal infection					
1 (Langhendries 1993)	10/10 (100%)	12/12 (100%)	RR 1.00 (0.84 to 1.18)	0 fewer per 1000 (160 fewer to 180 more)*	Low
Mortality					
1 (Langhendries 1993)	0/10 (0%)	0/12 (0%)	NC	NC	Low
Kidney damage (nephrotoxicity)[a]					
1 (Langhendries 1993)	0/10 (0%)	0/12 (0%)	NC	NC	Low
Hearing damage (ototoxicity)[b]					
1 (Langhendries 1993)	0/10 (0%)	0/12 (0%)	NC	NC	Low

NC not calculable, RR relative risk

* Calculated by the NCC-WCH technical team from data reported in the article

[a] Urinary levels of four low molecular weight proteins (albumin, beta-2-microglobulin, retinol binding proteins and Clara cell protein) and four kidney-derived enzymes (gamma-glutamyltransferase, alkaline phosphatase, alanine aminopeptidase and N-acetyl-beta-D-glucosaminidase) were used to assess damage to and functional integrity of proximal renal tubules, respectively. Fractional excretion of sodium and levels of phospholipid were also measured

[b] Ototoxicity was assessed using brainstem auditory evoked potentials (BEAPs) performed on day 0 and repeated on days 6 and 9

Table 9.13 Evidence profile for intravenous benzylpenicillin (25,000 IU/kg once every 12 hours compared to 50,000 IU/kg once every 12 hours) in very preterm babies (< 28 weeks' gestation, birthweight < 1200 g) with suspected infection in the first 3 days of life; all babies also received gentamicin (5 mg/kg every 48 hours)

Number of studies	Number of babies		Effect		Quality
	25,000 IU/kg of benzylpenicill in every 12 hours	50,000 IU/kg of benzylpenicill in every 12 hours	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Pharmacokinetics					
Peak serum penicillin concentration					
1 (Metsvah t 2007)	[a]	[a]	-	-	Very low
Trough serum penicillin concentration[c]					
1 (Metsvah t 2007)	[b]	[b]	-	-	Very low

MIC_{90} minimum inhibitory concentration required to inhibit the growth of 90% of organisms

[a] Dichotomous data not reported; actual peak serum concentrations (median) were: 50,000 IU/kg group (n = 8) 145.5 microgram/ml; 25,000 IU/kg group (n = 9) 58.90 microgram/ml; term babies (n = 23) 22.0 microgram/ml; adults (n = 6) 45 microgram/ml

[b] Dichotomous data not reported; actual trough serum concentrations (median) were: 50,000 IU/kg group (n = 8) 7.1 microgram/ml; 25,000 IU/kg group (n = 9) 3.4 microgram/ml; term babies (n = 23) 2.3 microgram/ml; adults (n = 6) not reported

[c] For a dose of 25,000 IU/kg of benzylpenicillin every 12 hours the median trough concentration was 3.4 microgram/ml. This is well above the MIC_{90} for group B streptococcus (MIC_{90}, 0.062 to 0.094 microgram/ml). This suggests that in this population of very preterm babies < 28 weeks' gestation, a dose of 25 000 IU/kg will be adequate throughout the dosing interval

Table 9.14 Evidence profile for intravenous benzylpenicillin (50,000 IU/kg) every 12 hours in preterm babies (< 32 weeks' gestation) with suspected infection in the first 3 days of life; all babies also received tobramycin or cefotaxime (dosage regimens not reported)

Number of studies	Proportion of simulated babies (n = 10,000 simulations on 167 samples from 20 babies)* receiving 50,000 IU/kg of benzylpenicillin every 12 hours	Effect		Quality
		Relative (95% confidence interval)	Absolute (95% confidence interval)	
Pharmacokinetics				
Probability of target attainment for pathogens with MICs of ≤4 mg/l, using Monte Carlo simulation (with the assumption that in preterm babies, at least 50% of the time, the concentration of benzylpenicillin remains above the MIC)[a]				
1 (Muller 2007)	100%	-	-	Very low

MIC minimum inhibitory concentration

[a] The estimates of the pharmacokinetic parameters and measures of dispersion from the study were used to simulate various dosing regimens and obtain the percent fT > MIC as a function of MIC. The simulated subjects were based on 167 data points from 20 patients and reasonable, justified, gestational-age appropriate assumptions about the variability between babies. A Monte Carlo simulation takes repeated samples (n=10,000) from these distributions to give the result reported

Table 9.15 Advantages and disadvantages of antibiotic regimens used for empirical treatment of early-onset neonatal infection in the United Kingdom

	Evidence identified for inclusion in the guideline review		No evidence identified for inclusion in the guideline but used in clinical practice in the UK			
	Benzylpenicillin plus gentamicin[a]	**Ampicillin (or amoxicillin)[b] plus gentamicin[a]**	**Benzylpenicillin plus ampicillin (or amoxicillin)[b]**	**Cefotaxime monotherapy**	**Ampicillin (or amoxicillin)[b] plus cefotaxime**	**Co-amoxiclav monotherapy (amoxicillin plus clavulanic acid)[c]**
Spectrum	Benzylpenicillin is narrow-spectrum (an advantage in terms of reducing development of antibiotic resistance)	Ampicillin and amoxicillin are broad spectrum compared to benzylpenicillin (a disadvantage in terms of promoting development of antibiotic resistance)	Ampicillin and amoxicillin are broad spectrum compared to benzylpenicillin (a disadvantage in terms of promoting development of antibiotic resistance)	Cefotaxime is broad-spectrum compared to benzylpenicillin (a disadvantage in terms of promoting development of antibiotic resistance)	Ampicillin, amoxicillin and cefotaxime are broad-spectrum compared to benzylpenicillin (a disadvantage in terms of promoting development of antibiotic resistance)	Amoxicillin is broad spectrum compared to benzylpenicillin (a disadvantage in terms of promoting development of antibiotic resistance)
Coverage	95–97% coverage based on UK data (excluding CONS)[d] CONS is the major non-susceptible organism, but is not very relevant in early-onset neonatal infection (because it is thought to be due to contamination of blood samples) and, in any case, there will be an opportunity to change to a different antibiotic regimen at 36 hours after presentation if required	Good coverage in the UK Provides optimal cover for listeria Ampicillin or amoxicillin might treat Gram-negative meningitis (such as *Escherichia coli* meningitis)	99% coverage based on UK data (excluding CONS)[e]	96% coverage based on UK data (excluding CONS)[e] Does not cover for listeria or *Enterococcus* species (the UK data did not include many listeria infections) Good CSF penetration, listeria meningitis	100% coverage based on UK data (excluding CONS)[e] Provides cover for listeria and most *Enterococcus* species Good CSF penetration, which makes it good for treating bacterial meningitis other than listeria meningitis	Good coverage in the UK (includes cover for *Staphylococcus aureus*)
	Problems with gentamicin resistance may occur in community settings, but less likely in hospital settings If the baby has early-onset *Escherichia coli* meningitis the combination of benzylpenicillin and gentamicin will be inadequate (contrast with ampicillin or amoxicillin plus gentamicin, which will be better as empirical treatment in this situation)					
Need for therapeutic drug monitoring	For gentamicin	For gentamicin			No	No
Care setting	Hospital or NICU	Hospital or NICU	Hospital or NICU	Hospital or NICU	Hospital or NICU	Hospital or NICU
Cost	Benzylpenicillin net price for 600mg vial is 95p	Ampicillin net price for 500mg vial is £7.83	Benzylpenicillin net price for 600mg vial is 95p	Cefotaxime net price for 500mg vial is £2.14	Ampicillin net price for 500mg vial is £7.83	Co-amoxiclav IV injection 500/100 powder (amoxicillin

	Gentamicin IV infusion net price for 10ml (10mg) vial is£1.80 Both antibiotics would need to be administered intravenously; associated staff costs comprise cost of two nurses × dose frequency; also gentamicin monitoring would require extra blood sampling Infrequent administration of gentamicin is possible if dosage regimen is right Need to follow NPSA guidance on the safe use of gentamicin in neonatal services[f] (because of common prescribing errors) makes gentamicin administration labour	Amoxicillin net price for 250mg vial is 32p net price for 500mg vial is 66p net price for 1g vial is £1.16 Gentamicin IV infusion net price for 10ml (10mg) bottle is £1.80 Both antibiotics would need to be administered intravenously; associated staff costs comprise cost of two nurses × dose frequency; also gentamicin monitoring would require extra blood sampling Infrequent administration of gentamicin is possible if dosage regimen is right Need to follow guidance on th of gentamicin i services[f] (because of	Ampicillin net price for 500-mg vial is £7.83 Amoxicillin net price for 250mg vial is 32p net price for 500mg vial is 66p net price for 1g vial is £1.16 Both antibiotics would need to be administered intravenously; associated staff costs comprise cost of two nurses × dose frequency	net price for 1g vial is £4.31 net price for 2g vial is £8.57 The antibiotic would need to be administered intravenously; associated staff costs comprise cost of two nurses × dose frequency Administration of one drug is easier than administration of two drugs (an advantage of monotherapy)	Amoxicillin net price for 250mg vial is 32p net price for 500mg vial is 66p net price for 1g vial is £1.16 Cefotaxime net price for 500mg vial is £2.14 net price for 1g vial is £4.31 net price for 2g vial is £8.57 Both antibiotics would need to be administered intravenously; associated staff costs comprise cost of two nurses x dose frequency	500 mg as sodium salt, clavulanic acid 100 mg as potassium salt) for reconstitution, net price per vial is £1.21 IV injection 1000/200 powder (amoxicillin 1 g as sodium salt, clavulanic acid 200 mg as potassium salt) for reconstitution, net price per vial is £2.63 The antibiotic would need to be administered intravenously; associated staff costs comprise cost of two nurses × dose frequency Administration of one drug is easier than administration of two drugs (an advantage of monotherapy)
	administration labour intensive (and,	services[f] (because of common prescribing				

	Evidence identified for inclusion in the guideline review		No evidence identified for inclusion in the guideline but used in clinical practice in the UK			
	Benzylpenicillin plus gentamicin[a]	**Ampicillin (or amoxicillin)[b] plus gentamicin[a]**	**Benzylpenicillin plus ampicillin (or amoxicillin)[b]**	**Cefotaxime monotherapy**	**Ampicillin (or amoxicillin)[b] plus cefotaxime**	**Co-amoxiclav monotherapy (amoxicillin plus clavulanic acid)[c]**
	therefore, costly), but some aspects of the NPSA checklist might apply as good practice to all drugs to avoid errors	errors) makes gentamicin administration labour intensive (and, therefore, costly), but some aspects of the NPSA checklist might apply as good practice to all drugs to avoid errors				
Adverse effects	Potential side effects of gentamicin (mainly damage to hearing and kidneys); long-term risks uncertain but probably limited by effective monitoring	Potential side effects of gentamicin (mainly damage to hearing and kidneys); long-term risks uncertain but probably limited by effective monitoring	Unnecessary duplication of treatment (benzylpenicillin may not be needed in addition to ampicillin or amoxicillin)			Concentration of components varies between different parts of the body (uncertain pharmacology)

CONS coagulase-negative Staphylococci, CSF cerebrospinal fluid, IV intravenous, NICU neonatal intensive care unit, NPSA National Patient Safety Agency

[a] An aminoglycoside other than gentamicin (for example, amikacin) might be used in certain settings

[b] Ampicillin and amoxicillin have equivalent roles in each context

[c] The addition of clavulanic acid in this product is to keep amoxicillin active

[d] Data from Muller-Pebody 2011 and Vergnano 2011

[e] Data from Muller-Pebody 2011

[f] NPSA guidance and checklist available at http://www.nrls.npsa.nh Web/getresource.axd?AssetID=66284&type=full&servicetype=Attachment)

Evidence statements

Comparison between different antibiotics or combinations of antibiotics

There were no differences in rates of treatment failure, 7-day mortality, neonatal intensive care unit (NICU) mortality, or colonisation with ampicillin-resistant Gram-negative bacteria between babies treated for suspected early-onset neonatal infection with benzylpenicillin plus gentamicin and those treated with ampicillin plus gentamicin.

There was, however, a **lower rate of NICU mortality in babies less than 26 weeks** of gestation who received **ampicillin plus gentamicin compared to those who received benzylpenicillin and gentamicin.** Treatment with ampicillin plus gentamicin resulted in more babies **being colonised with *Staph haemolyticus* and *Staph hominis*, and longer durations of colonisation**, compared with treatment with benzylpenicillin plus gentamicin. Treatment with ampicillin plus gentamicin **did not affect the number of babies colonised with *Klebsiella pneumoniae*, but those who were colonised had longer durations of colonisation** than did babies treated with benzylpenicillin plus gentamicin. Treatment with ampicillin plus gentamicin**resulted in fewer babies being colonised with *Enterococcus* species and *Staph aureus*, and shorter durations of colonisation,** compared to treatment with benzylpenicillin plus gentamicin. Treatment with ampicillin plus gentamicin**did not affect the number of babies colonised with ampicillin-resistant *Acinetobacter* species, *Acinetobacter* species in general, or *Enterobacter cloacae*, but those colonised with ampicillin-resistant *Acinetobacter* species had shorter durations of colonisation than did babies treated with benzylpenicillin plus gentamicin (low quality evidence).**

There **was no difference in cure rates between babies** who received benzylpenicillin plus gentamicin for suspected early-onset neonatal infection and those who received ceftazidime **(low qualityevidence).**

There were **no differences in nephrotoxicity or ototoxicity** between babies who received gentamicin forsuspected early-onset neonatal infection and those who received tobramycin**(low quality evidence).**There were no differences in cure rates or mortality during treatment between babies who receivedticarcillin plus clavulanic acid for suspected early-onset neonatal infection and those who receivedgentamicin and piperacillin (low quality evidence).

Comparison between different dosing regimens of the sameantibiotics

No cases of ototoxicity were reported in near-term and term babies who received gentamicin every 24hours daily for treatment of suspected early-onset neonatal infection, nor in those who receivedgentamicin every 12 hours (low quality evidence).

No cases of nephrotoxicity were reported in very low birthweight or preterm babies who receivedgentamicin every 48 hours for suspected early-onset neonatal infection, nor in those who receivedgentamicin every 18–24 hours (low quality evidence).

No cases of ototoxicity were reported in one study **based on very low birthweight babies who receivedgentamicin every 48 hours for suspected early-onset neonatal infection, nor in those who receivedgentamicin every 24 hours**(low quality evidence).

In **a separate study based on preterm babies therewas no difference in ototoxicity rates between babies who received gentamicin every 48 hours andthose who received gentamicin every 18–24 hours** (low quality evidence).

There was **no difference in cure rates between near-term or term babies who received amikacin every24 hours for suspected early-onset neonatal infection and those who received amikacin every 12hours.** No cases of mortality, nephrotoxicity or ototoxicity were reported in either treatment arm (lowquality evidence).

Pharmacokinetic outcomes

A 12-hourly gentamicin dosing regimen at 2.5 mg/kg/dose is more likely to lead to high troughconcentrations of more than 2 microgram/ml compared to 4 mg/kg given at 24-hour intervals (lowquality evidence).Antibiotics for early-onset neonatal infectionIn babies who received a 4 mg/kg loading dose of gentamicin compared with babies who received

astandard initial dose of 2.5 mg/kg, the evidence relating to trough concentrations is not relevant toclinical practice because some of the trough concentrations were measured at 12 and 18 hours,rather than at 24 hours (low quality evidence).In term babies, a gentamicin dosage of 2.5 mg/kg 12 hourly was associated with a smaller proportionof babies attaining a useful peak concentration compared to a dose of 4 mg/kg every 24 hours (lowquality evidence).

In very low birthweight babies, peak serum gentamicin concentrations of less than 5 microgram/mlwere more common in babies receiving 2.5–3 mg/kg/dose every 24 hours than in babies receiving5 mg/kg/dose every 48 hrs (low quality evidence).

Babies with very low birthweight who received 5 mg/kg/dose of gentamicin every 48 hours were morelikely to have a peak concentration in the therapeutic range than were babies who received 2.5–3mg/kg every 24 hours (low quality evidence).Babies who received 4.5 mg/kg of gentamicin as the first dose were more likely to attain peak serumconcentrations of more than 5 microgram/ml than were babies who received 2.5 mg/kg as the firstdose (low quality evidence).A benzylpenicillin dosage of 25,000 IU/kg is safe and effective in preterm babies (very low qualityevidence). No evidence was identified for benzylpenicillin in term babies.

Quality of evidence

All the evidence available from RCTs was of low quality, although this did not prevent the GDG making strong recommendations because there was no evidence to direct a change from the most frequently used antibiotic regimen for empirical treatment of early-onset neonatal infection(see below). No RCT evidence was identified for some antibiotic regimens in current practice, and few of the outcomes prioritised by the GDG were examined for relevant treatment comparisons. **The included studies were generally small and evidence was not available comprehensively for babies of different gestational ages.** The GDG made research recommendations to address these knowledge gaps, including specification of consensus definitions of core exposures and outcomes required for research to evaluate the clinical and cost effectiveness of antibiotics for the prevention or treatment of early-onset neonatal infection.

Benzylpenicillin plus gentamicin compared with ampicillin plus gentamicin

In terms of **mortality outcomes**, the **only statistically significant difference between an antibiotic regimen combining benzylpenicillin with gentamicin and a regimen combining ampicillin with gentamicin was a protective effect of ampicillin plus gentamicin for survival of babies under 28 weeks' gestation receiving care in a NICU.The GDG – Guideline Development Group highlighted the small number of babies that were evaluated and the potential for reporting bias (in that results for other gestational age groups were not reported, so the reported finding might have arisen from a *post hoc* analysis rather than preplanned analyses stratified by gestational age). The GDG also considered that the choice of antibiotic regimen would be unlikely to be the only contributing factor to the difference in mortality rates in these preterm babies. Several of the bacteria reported in colonisation results were considered to be atypical of the bacteria that cause early-onset neonatal infection. For example, Staphyloccoccus species and *Acinetobacter* species are possible contaminants, and Enterobacter species might be related to hospital-acquired infections. The GDG believed that even if the excess mortality in the benzylpenicillin plus gentamicin group was due to early-onset neonatal infection, i**t was plausible that there had been an outbreak of Gram-negative bacteria in the NICU, and that other factors not addressed by the randomisation process might skew the results in this small population

(for example, there was a possibility of seasonal effects due to the sequential [cross-over], rather than parallel, study design). **The GDG emphasised that for clinically important outcomes, such as 7-day mortality, there was no statistically significant difference between the antibiotic regimens, and so the study did not provide evidence to support a change in practice away from the commonly used narrow-spectrum regimen of benzylpenicillin plus gentamicin. The GDG also noted that the study provided clear evidence of different antibiotic drugs selecting for different micro-organisms**. Since none of the colonisation results reported in this study was found by the GDG to be particularly reassuring or worrying, the different selection pressures exerted by the different antibiotic regimens did not prevent the GDG making recommendations for the use of narrow-spectrum antibiotics.

Benzylpenicillin plus gentamicin compared with ceftazidime

Although cure rate was reported in the one RCT that contributed evidence for this treatment comparison, **no statistically significant differences were observed**. The study authors reported that benzylpenicillin plus gentamicin was the usual first-line antibiotic treatment in the unit where the studywas conducted. However, the GDG did not consider the treatment comparison to be relevant to UKpractice because ceftazidime is reserved for use against *Pseudomonas* species. The GDG also notedthat the source of funding was not reported in the article (the group suspected that healthcareprofessionals may have been funded by a pharmaceutical company to participate in the study).

Benzylpenicillin pharmacokinetics

The GDG considered that the evidence from the two non-randomised studies that evaluated thepharmacokinetics of benzylpenicillin in preterm babies was of very low quality. Nevertheless, the
GDG's view was that the studies demonstrated that a benzylpenicillin dosage of 25,000 IU/kg every12 hours is safe and effective in such babies. No evidence was identified for benzylpenicillinpharmacokinetics in term babies.

Other considerations

The GDG considered whether cultural practices associated with particular ethnic groups mightinfluence the incidence of specific early-onset neonatal bacterial infections. For example, the GDGdiscussed whether increased geographical mobility might increase the prevalence in England andWales of culinary practices or dietary habits associated with listeriosis, which is caused by listeria(*L monocytogenes*). Antenatal care (NICE clinical guideline 62, 2008) highlights the risks to pregnantwomen, unborn babies and newborn babies associated with listeriosis, which can be caused by theconsumption of unpasteurised milk, ripened soft cheese (such as Camembert, Brie and blue-veinedcheese)and pâté. Although the GDG identified no evidence of an increased prevalence of listeriosis inthe studies reviewed for the guideline, the GDG's view was that benzylpenicillin and amoxicillin areboth suitable for the empirical treatment of suspected early-onset neonatal infection even whenlisteria is a potential pathogen. The GDG decided to recommend the use of benzylpenicillin plusgentamicin as empirical treatment for early-onset neonatal bacterial infections and not ampicillin plusgentamicin because benzylpenicillin has the advantage of being a narrow-spectrum antibiotic andprovides cover for a high percentage of pathogens relevant to the UK, including GBS.Furthermore, the recommendation to give benzylpenicillin plus gentamicin as empirical treatment forearly-onset neonatal infection should not disadvantage any ethnic group in terms of access toappropriate antibiotic treatment. Should listeria be positively identified, however, the GDG recognisedthat a change of antibiotic regimen to include amoxicillin would be appropriate.

Key conclusions

The GDG considered that the evidence included in the guideline review for the antibiotic regimensinvolving ceftazidime, ticarcillin plus clavulanic acid, and piperacillin was not relevant to the UK settingand the group chose not make recommendations in relation to these antibiotics. **The evidence relatingto benzylpenicillin, ampicillin, gentamicin and amikacin was, however, considered to be relevant toclinical practice in the UK.The GDG was aware that benzylpenicillin and gentamicin are the two most commonly prescribeddrugs in UK neonatal units (Turner 2009; this comparison is with all drugs used in neonatal units, notjust antibiotics).In terms of antibiotic treatment regimens for early-onset neonatal infection, the GDGidentified the following as representing variations in current clinical practice in the UK:**

• benzylpenicillin plus gentamicin

• ampicillin (or amoxicillin) plus gentamicin

• benzylpenicillin plus amoxicillin

• cefotaxime monotherapy

• ampicillin (or amoxicillin) plus cefotaxime

• co-amoxiclav monotherapy (amoxicillin plus clavulanic acid).

The GDG noted that ampicillin and amoxicillin have equivalent roles in each context, and that incertain settings an aminoglycoside other than gentamicin (for example amikacin) might be used.

Based solely on the evidence identified for inclusion in the guideline, the GDG's initial view was thatthere was no reason to direct a change in practice away from the most commonly used antibioticregimen of benzylpenicillin plus gentamicin. Despite the lack of RCT evidence identified in relation toantibiotic regimens involving amoxicillin, cefotaxime and co-amoxiclav, the GDG considered thepotential advantages and disadvantages of each regimen in detail. Specific criteria were:

• the spectrum of antibiotic activity (narrow or broad, with broad-spectrum antibioticsbeing more likely to exert selective pressure on micro-organisms, thus promoting thedevelopment of antibiotic resistance)

• coverage against the most frequent causes of early-onset neonatal infection

• the need for therapeutic drug monitoring

• care setting

• cost

• adverse effects.

The GDG's conclusions in relation to each of these criteria are summarised in Table 9.15. **The GDG'soverall conclusion was that the combination of benzylpenicillin and gentamicin is the preferredempirical treatment for early-onset neonatal infection.**

First, the evidence from surveillance data andclinical practice indicates that this combination would successfully treat the vast majority of cases ofearly-onset neonatal infection.

Second, this combination has the major advantage of having a narrowspectrum of activity. The GDG was aware that antibiotic resistance is not commonly induced withgentamicin

use. With gentamicin there is a need for therapeutic drug monitoring. However, thedosage interval recommendation in this guideline (usually 36 hours) is such that in many cases only asingle dose of gentamicin would be given. This would not only reduce overall antibiotic usage, butwould in many cases mean that therapeutic monitoring need not be undertaken as the first monitoringsample would be taken prior to the second dose of gentamicin. Monitoring provides a means ofreducing the risk of gentamicin toxicity. The GDG considered the possible concerns regarding anassociation between gentamicin and ototoxicity.A prospective birth-cohort study estimated the prevalence of the m.1555A→G mutation to have aprevalence of 1 in 520 (or 0.19%; 95% confidence interval [CI], 0.10 to 0.28) in a population of babiesborn in 1991–1992 in the UK (Bitner-Glindzicz 2009). This mutation has been associated with a veryhigh risk of deafness following gentamicin administration. The association between gentamicin anddeafness may not be relevant to neonates because of pharmacokinetic and pharmacodynamicdifferences between neonates and older age groups. Gentamicin may not penetrate into the cochleaand the neonatal cochlea may use different metabolic pathways. In support of the suggestion thatgentamicin does not pose a similar risk in neonates to older age groups is global experience withaminoglycosides in newborn babies. The GDG noted, however, that benzylpenicilin and gentamicinhave been in widespread use in neonatal practice for many years, and very large numbers of babiesreceive gentamicin every year. Evidence that gentamicin may cause deafness when administered in theneonatal period was lacking. Screening for sensorineural deafness in preterm babies has indicated avery low incidence despite widespread gentamicin usage. Evidence in relation to therapeutic drugmonitoring, and the GDG's recommendations on this topic, are presented in Chapter 11.With respect to the dosage regimen for benzylpenicillin, the GDG noted that the dosages evaluated inthe evidence were lower than those commonly used in clinical practice according to the GDG'sexperience. The GDG members noted further that there was a lack of evidence regarding theAntibiotics for suspected infectionelimination rate of benzylpenicillin in term babies, but based on their knowledge and experience thegroup believed that there was no risk of toxicity with benzylpenicillin for any baby even if the dosagewere to be increased further, and this justified the GDG's recommendation for a more frequent dosingschedule in very ill babies.

The evidence presented supports the GDG's position that therecommended dose is likely to be adequate for an uncomplicated septicaemia with a susceptiblebacteria. Because the effectiveness of treatment for septicaemia is time dependent, in severesepticaemia increased frequency of antibiotic dosing will improve the antibiotic action. A larger doseof antibiotic might be considered when the infection involves a different compartment of the body (forexample inside the blood-brain barrier, as in meningitis). The dosages recommended by the GDG areconsistent with those in the summary of product characteristics (SPC; which includes a 'double dose'for babies with meningococcal meningitis). The GDG noted that the double dose is also used inclinical practice to treat GBS meningitis, the rationale being that the MIC for GBS is similar to, orpossibly even higher than, that for meningococcus.

With respect to the dosage regimen for gentamicin, the GDG recommended an initial dose of 5 mg/kgto achieve a peak blood gentamicin concentration of 8 mg/l. **The GDG's recommendations arestrongly supported by evidence reviewed for the guideline showing that an initial dose of 4–5 mg/kg(and no further administration of gentamicin for 48 hours) is effective and safe, even in very lowbirthweight babies (600–1500g).**Considering the practicality of administering gentamicin (which isoften associated with dosing errors in neonatal units), **the GDG concluded that a pragmatic approachto**

the selection of the starting dose for gentamicin within the range 4–5 mg/kg would be 5 mg/kg,since this integer value would be less susceptible to errors when calculating the dose for an individualbaby (based on the baby's weight). The GDG's recommendation is in accordance with the SPCs forgentamicin, which for newborn babies recommend 4–7 mg/kg/day administered in a single dose.However, the SPCs do not yet reflect the evidence reviewed for the guideline showing that the lowerend of the dosage range recommended in the SPCs is to be preferred. The GDG also noted thatcurrent practice varies considerably. A recent survey of gentamicin dosage regimens and approachesto therapeutic monitoring for gentamicin used in 43 UK neonatal units (Kadambari 2011) showed that:

• 24 different combinations of dose, timing of dose and timing of monitoring are currentlyin use.

• Dosages as low as 2.5–3.5 mg/kg are used in some units, although the vast majority ofunits (approximately 90% in babies at 24–28 weeks' gestation, and an even higherproportion in babies at more than 28 weeks of gestation) use a dosage of 4.5–5 mg/kg.

• Dosage intervals vary considerably; for example, in babies at 28 weeks of gestationdosage intervals of 12, 18, 24, 36 and 48 hours were being used at the time of draftingthis guideline.Thus, the GDG's recommendations should reduce variations in practice while ensuring theeffectiveness and safety of gentamicin dosage regimens for early-onset neonatal infection.The GDG was aware of the need to document gentamicin administration and therapeutic drugmonitoring in accordance with guidance issued by the National Patient Safety Agency (NPSA) inFebruary 2010 on the safe use of gentamicin in neonatal services (see Safer use of intravenousgentamicin for neonates [PDF file]). The GDG believed that such documentation would facilitatedecisions regarding any further doses of gentamicin to be given, any changes from empiricaltreatment to cover specific bacteria confirmed by blood or CSF cultures, and discharge of well babiesfrom hospital. The GDG recognised that expert microbiological advice based on local surveillancedata might also need to be considered as part of the decision to change antibiotic regimen. Thejustification for the GDG's recommended gentamicin dosing interval of 36 hours even in pretermbabies (despite no direct evidence being available to support this) was that, on balance, the benefitsof treatment would outweigh the risks of not treating. The GDG further recognised that babies withculture-proven Gram-negative infection or who appear to be very ill despite antibiotic treatment havingstarted, would be exceptions to this rule, and that clinical judgment would be required to decidewhether the baby needed a second dose of gentamicin before 36 hours had passed. In those babiesfor whom there is microbiological evidence of Gram-negative bacterial sepsis, this decision would alsoinclude whether there was a need to add to the antibiotic regimen an antibiotic providing cover for thispathogen (for example cefotaxime). **The GDG's consensus was that if Gram-negative infection was confirmed, benzylpenicillin should be stopped.** The GDG also made a research recommendation to investigate optimal antibiotic dosage regimens and specifically prioritised preterm babies for consideration as part of this research. In the GDG's view, the evidence included in the guideline review was from studies that were insufficiently powered to examine adverse events of antibiotic treatment, and no long-term outcomes were reported. The GDG therefore made a further research recommendation to address this. The GDG also noted that there was little evidence regarding the optimal antibiotic treatment cover for early-onset neonatal meningitis, and so the group recommended further research on this topic to include consideration of the choice of antibiotic regimen and the duration of antibiotic treatment.

1. Antibiotics for early-onset neonatal infection: antibiotics for the prevention and treatment of early-onset neonatal infection (NICE) August 2012.

-Evidence Update June 2014.

1.5 Investigations before starting antibiotics in the baby

Full blood count

During the development of NICE CG149, peripheral white blood cell count, absolute neutrophil count and immature to total neutrophil ratio (I:T ratio) were considered for ruling in early-onset neonatal infection in asymptomatic babies with at least one risk factor. However, the health economic analysis conducted for the guideline did not provide robust evidence of the cost effectiveness of full blood count in asymptomatic babies, so NICE CG149 does not recommend its use. In addition, the diagnostic test accuracy of full blood count was not sufficiently strong to recommend its use at presentation in babies about to start antibiotic treatment.

Hornik et al. (2012) conducted a retrospective cohort study to evaluate the accuracy of full blood count in diagnosing early-onset infection in neonates. Demographic, culture (blood, urine or cerebrospinal fluid), and full blood count data were obtained for neonates admitted to 293 US neonatal intensive care units over a 13 year period. Early-onset infection was defined as a positive culture during the first 3 days of life. A total of 166,092 neonates with 171,376 cultures were identified; 2177 (1.3%) positive cultures in 2164 (1.3%) neonates were recorded.

Low white blood cell count (<8800/mm3) was associated with an increased odds of culture-proven early-onset infection (OR=1.53, 95% CI 1.13 to 2.06), but high white blood cell count did not increase the odds of infection.An absolute neutrophil count of less than 4134/mm3, a platelet count of less than 147,000/mm3, and an I:T ratio of more than 0.24 were also all associated with early-onset infection (data reported graphically). The sensitivity of the blood count indices for early-onset infection was low, with the highest sensitivity observed for an I:T ratio of more than 0.24 (49.2%). Specificity was generally higher, with the lowest specificity for an absolute neutrophil count of less than 4134/mm3 (74.3%). The positive likelihood ratios ranged from 1.5 for a platelet count of less than 147,000/mm3, to 2.5 for an I:T ratio of more than 0.24. The negative likelihood ratios ranged from 0.6 for an I:T ratio of more than 0.24, to 1 for a platelet count of less than 147,000/mm3.

Limitations of the evidence include that it was a retrospective analysis and that the database lacked information on infants' previous exposure to antibiotics before culture samples were taken. No information was available on whether the infants were symptomatic at the time the culture was taken. Little data was available on maternal risk factors unrelated to infection that might affect neonatal blood counts (for example, maternal hypertension and preeclampsia, which may cause neonatal neutropenia and thrombocytopenia).

The evidence suggests that full blood count indices may not be sufficiently sensitive to rule out early-onset infection in neonates. This evidence is unlikely to have an impact on NICE CG149, which does not recommend full blood count for the diagnosis of early-onset neonatal infection.

Key reference

Hornik CP, Benjamin DK, Becker KC et al. (2012) Use of the complete blood cell count in early-onset neonatal sepsis. The Pediatric Infectious Disease Journal 31: 799–802 [NIH Public Access author manuscript – full text]

2. Centers for Disease Control and Prevention, CDC.

Prevention of Perinatal Group B Streptococcal Disease, Revised Guidelines from CDC, MMWR, Morb Mortal Wkly Rep. 2010; 59:RR-10

3.

TABLE 1. Evidence-based rating system used to determine strength of recommendations

Category	Definition	Recommendation
Strength of recommendation		
A	Strong evidence for efficacy and substantial clinical benefit	Strongly recommended
B	Strong or moderate evidence for efficacy but only limited clinical benefit	Generally recommended
C	Insufficient evidence for efficacy or efficacy does not outweigh possible adverse consequences	Optional
D	Moderate evidence against efficacy or for adverse outcome	Generally not recommended
E	Strong evidence against efficacy or for adverse outcome	Never recommended
Quality of evidence supporting recommendation		
I	Evidence from at least one well-executed randomized, controlled trial or one rigorously designed laboratory-based experimental study that has been replicated by an independent investigator	
II	Evidence from at least one well-designed clinical trial without randomization, cohort or case-controlled analytic studies (preferably from more than one center), multiple time-series studies, dramatic results from uncontrolled studies, or some evidence from laboratory experiments	
III	Evidence from opinions of respected authorities based on clinical or laboratory experience, descriptive studies, or reports of expert committees	

Source: Adapted from LaForce FM. Immunizations, immunoprophylaxis, and chemoprophylaxis to prevent selected infections. US Preventive Services Task Force. JAMA 1987;257:2464–70.

Secondary Prevention Among Infants

To detect potential sepsis cases in newborns as early as possible, newborns should be managed according to the algorithm provided (Figure 9).The following are key components of the neonatal management algorithm:

• **Any newborn with signs of sepsis** should receive a full diagnostic evaluation and receive antibiotic therapy pending the results of the evaluation. **The evaluation should include a blood culture; a CBC including white blood cell differential and platelet count; a chest radiograph if any abnormal respiratory signs are present; and a lumbar puncture if the newborn is stable** enough to tolerate the procedure and sepsis is suspected. **Therapy** for the infant should include antimicrobial **agents active against GBS (including intravenous ampicillin) as well as other organisms that might cause neonatal sepsis, such as E. coli (AII).**

• **Well-appearing newborns whose mothers had suspected chorioamnionitis should undergo a limited evaluation and receive antibiotic therapy pending culture results (AII).The evaluation should include a blood culture and a CBC including white blood cell differential and platelet count; no chest radiograph or lumbar puncture is ne**eded. Consultation with obstetric providers to assess whether chorioamnionitis was suspected is important to determine neonatal management **(CIII).**

• Well-appearing infants whose mothers had no chorioamnionitis and no indication for GBS prophylaxis should be managed according to routine clinical care (CIII).

• Well-appearing infants of any gestational age whose mother received adequate intrapartum GBS prophylaxis (≥4 hours of penicillin, ampicillin, or cefazolin before delivery) should be observed for ≥48 hours, and no routine diagnostic testing is recommended (BIII). Such infants can be discharged home as early as 24 hours after delivery, assuming that other discharge criteria have been met, ready access to medical care exists, and that a person able to comply fully with instructions for home observation will be present (CIII).

• For well-appearing infants born to mothers who had an indication for GBS prophylaxis but received no or inadequate prophylaxis, if the infant is well-appearing and ≥37 weeks and 0 days' gestational age and the duration of membrane rupture before delivery was <18 hours, then the infant should be observed for ≥48 hours, and no routine diagnostic testing is recommended (BIII). If the infant is well-appearing and either <37 weeks and 0 days' gestational age or the duration of membrane rupture before delivery was ≥18 hours, then the infant should undergo a limited evaluation and observation for ≥48 hours (BIII).

The following key changes were made from the 2002 guidelines:

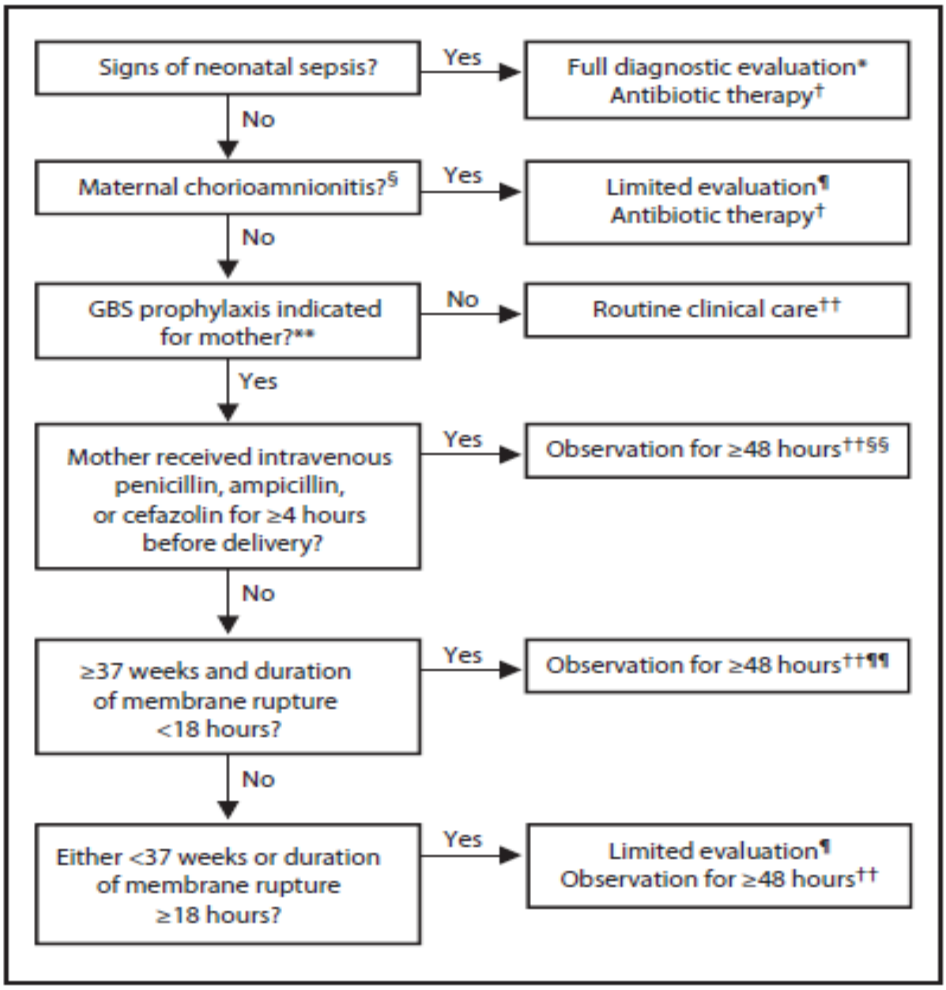
• **The algorithm now applies to all newborns.**

• The definition of adequate intrapartum antibiotic prophylaxis is clarified as ≥4 hours of IV penicillin, ampicillin, or cefazolin before delivery (AII). All other agents or durations are considered inadequate for purposes of neonatal management.

• **Well-appearing infants whose mother had an indication for GBS prophylaxis but received no or inadequate intrapartum antibiotics can be managed with observation for ≥48 hours, unless the infant is <37 weeks and 0 days' gestational age or membranes were ruptured ≥18 hours before delivery, in which case a limited evaluation and observation for ≥48 hours is recommended (BIII).**

• **Well-appearing infants with a gestational age of 35–36 weeks whose mothers received adequate intrapartum antibiotic prophylaxis do not routinely require diagnostic evaluations (CIII).**

FIGURE 9. Algorithm for secondary prevention of early-onset group B streptococcal (GBS) disease among newborns



* Full diagnostic evaluation includes a blood culture, a complete blood count (CBC) including white blood cell differential and platelet counts, chest radiograph (if respiratory abnormalities are present), and lumbar puncture (if patient is stable enough to tolerate procedure and sepsis is suspected).

† Antibiotic therapy should be directed toward the most common causes of neonatal sepsis, including intravenous ampicillin for GBS and coverage for other organisms (including *Escherichia coli* and other gram-negative pathogens) and should take into account local antibiotic resistance patterns.

§ Consultation with obstetric providers is important to determine the level of clinical suspicion for chorioamnionitis. Chorioamnionitis is diagnosed clinically and some of the signs are nonspecific.

¶ Limited evaluation includes blood culture (at birth) and CBC with differential and platelets (at birth and/or at 6–12 hours of life).

** See table 3 for indications for intrapartum GBS prophylaxis.

†† If signs of sepsis develop, a full diagnostic evaluation should be conducted and antibiotic therapy initiated.

§§ If ≥37 weeks' gestation, observation may occur at home after 24 hours if other discharge criteria have been met, access to medical care is readily available, and a person who is able to comply fully with instructions for home observation will be present. If any of these conditions is not met, the infant should be observed in the hospital for at least 48 hours and until discharge criteria are achieved.

¶¶ Some experts recommend a CBC with differential and platelets at age 6–12 hours.

3.Policy Statement-Recommendations for the Prevention of Perinatal Group B sterptococcal (GBS) Disease COMMITTEE ON INFECTIOUS DISEASES AND COMMITTEE ON FETUS AND NEWBORN, PEDIATRICS Volume 128, Number 3, September 2011

Abstract The Centers for Disease Control and Prevention (CDC) guidelines for the prevention of perinatal group B streptococcal (GBS) disease were initially published in 1996. The American Academy of Pediatrics (AAP) also published a policy statement on this topic in 1997. In 2002, the CDC published revised guidelines that recommended universal antenatal GBS screening; the AAP endorsed these guidelines and published recommendations based on them in the 2003 *Red Book*. Since then, the incidence of early-onset GBS disease in neonates has decreased by an estimated 80%. However, in 2010, GBS disease remained the leading cause of early-onset neonatal sepsis. The CDC issued revised guidelines in 2010 based on evaluation of data generated after 2002. These revised and comprehensive guidelines, which have been endorsed by the AAP, reaffirm the major prevention strategy— universal antenatal GBS screening and intrapartum antibiotic prophylaxis for culturepositive and high-risk women—and include new recommendations for laboratory methods for identification of GBS colonization during pregnancy, algorithms for screening and intrapartum prophylaxis for women with preterm labor and premature rupture of membranes, updated prophylaxis recommendations for women with a penicillin allergy, and a revised algorithm for the care of newborn infants. The purpose of this policy statement is to review and discuss the differences between the 2002 and 2010 CDC guidelines that are most relevant for the practice of pediatrics.

4.Prevention and Management of Infants With Suspected or Proven Neonatal Sepsis MT. Brady, Richard A. Polin, PEDIATRICS Volume 132, Number 1, July **2013**

In 2010, the Centers for Disease Control and Prevention in collaboration with the American Academy of Family Physicians, American Academy of Pediatrics (AAP), American College of Nurse-Midwives, American College of Obstetricians and Gynecologists, and American Society for Microbiology published revised group B streptococcal (GBS) guidelines entitled "Prevention of perinatal group B streptococcal disease: **revised guidelines from CDC 2010" in the Morbidityand Mortality Weekly Report (MMWR).** The recommendations were endorsed by all the collaborating organizations including AAP after review by the Committee on Infectious Diseases (COID) and the Committee on Fetus and Newborn (COFN) and after AAP Board approval. In the report, a revised algorithm for "Secondary prevention of earlyonset group B streptococcal disease" was included. This algorithm represented the expert opinions of the technical working group (based on current literature available at that time). **In 2011, the COID and the COFN published a policy statement in Pediatrics that was in agreement with the 2010 GBS guidelines and included the same algorithm.**In the spring of **2012,** the **COFN published a clinical report containing management guidelines entitled "Management of neonates with suspected or proven early-onset neonatal sepsis." The 2012 COFN document includes guidance on laboratory evaluations and treatment duration, which were not addressed in the 2010 GBS prevention guidelines.**

The algorithms at the end of the COFN report differed from those in the 2010 guidelines published in the MMWR. The discordance in the algorithms prompted questions by the pediatric community as to which recommendations to follow. The purpose of this commentary is to clarify AAP policy. Discordant algorithms for secondary prevention of GBS were published in 2 separate policy statements.This commentary includes the algorithmthat has been approved as current AAP policy. Providing a singlealgorithm will

avoid confusion and ensure that the guidelinesachieve their desired effects.The COFN and the COID strongly support the recommendations made inthe 2010 prevention guidelines approved by the AAP and the othercollaborating organizations (secondary prevention of GBS algorithmrepresenting current AAP policy is attached in Fig 1). However, the COFNnotes that in some situations, other approaches might be consideredthat differ from guidance provided in the 2010 prevention guidelines**.The following recommendations include the recommendations from the2010 MMWR publication and those made by the COFN 2012:**

1. Neonates who have signs of sepsis should receive broad-spectrumantimicrobial agents.

2. Healthy-appearing preterm and term infants born to women withsuspected chorioamnionitis should receive a blood culture at birth, a complete blood count with differential 1/2 C-reactive protein at age 6 to 12 hours. These infants should be treated with broadspectrum antimicrobial agents.

3. For well-appearing infants ≥37 weeks' gestation whose mother did not have suspected chorioamnionitis, but who did have an indication for intrapartum antibiotic prophylaxis and did not receive at least 4 hours of intrapartum penicillin, ampicillin or cefazolin: a. The 2010 GBS prevention guidelines and the 2012 COFN statement agree that infants who are well appearing can be observed without additional testing if duration of rupture of membranes is <18 hours. The COFN believes that infants at 35 to 36 weeks' gestation can be treated similarly if the physical examination is normal. b. If duration of membrane rupture is ≥18 hours and IAP is inadequate,the 2010 GBS prevention guidelinesrecommend a limited evaluation(blood culture and completeblood cell [CBC] count with differentialat birth or 6 to 12 hoursof age) and hospital observationfor 48 hours. The COFN recommendshospital observation for48 hours in this circumstance(without further testing or cultures).However, when close observationis not possible, theCOFN recommends a laboratoryevaluation.

4. For well-appearing infants <37weeks' gestation whose mother didnot have suspected chorioamnionitis,but who did have an indication forIAP and did not receive adequateprophylaxis, the 2010 GBS preventionguidelines recommend a limitedevaluation (blood culture andCBC count) and hospital observationfor 48 hours. The COFN alsorecommends a limited evaluation,but no blood culture unless antibioticsare started because of abnormallaboratory data.

5. The 2010 GBS prevention guidelinesdo not address the duration of antibiotictherapy. The COFN makesrecommendations for the durationof antimicrobial therapy based onthe results of laboratory testing.Healthy-appearing infants withoutevidence of bacterial infection shouldreceive broad-spectrum antimicrobialagents for no more than 48 hours.In small preterm infants, somemay continue antibiotics for upto 72 hours while awaiting bacterialculture results.

Published data to support recommendationsfor prevention and managementof newborn sepsis are limited.However, success of the GBS preventionguidelines provides evidence that reductionsin early-onset GBS diseasehave been possible by the developmentof consensus guidelines with consistent implementation.The COFN's 2012 recommendations complement the 2010 GBS prevention guidelines by providing additional treatment information that is not addressed in the 2010 prevention guidelines. These should provide clinicians with guidance for optimal duration of antimicrobial therapy and reduce excess exposure to broad-spectrum antimicrobial therapy in healthy-appearing uninfected infants who had empirical antimicrobial therapy initiated.

Viited

Kokkuvõtte (abstract või kokkuvõtlikum info)	**Viide kirjandusallikale**
AbstractWith improved obstetrical management and evidence-based use of intrapartum antimicrobial therapy, early-onset neonatal sepsis is becoming less frequent. However, early-onset sepsis remains one of the most common causes of neonatal morbidity and mortality in the preterm population. The identification of neonates at risk for early-onset sepsis is frequently based on a constellation of perinatal risk factors that are neither sensitive nor specific. Furthermore, diagnostic tests for neonatal sepsis have a poor positive predictive accuracy. As a result, clinicians often treat well-appearing infants for extended periods of time, even when bacterial cultures are negative. The optimal treatment of infants with suspected early-onset sepsis is broad-spectrum antimicrobial agents (ampicillin and an aminoglycoside). Once a pathogen is identified, antimicrobial therapy should be narrowed (unless synergism is needed). Recent data suggest an association between prolonged empirical treatment of preterm infants (≥5 days) with broad-spectrum antibiotics and higher risks of late onset sepsis, necrotizing enterocolitis, and mortality. To reduce these risks, antimicrobial therapy should be discontinued at 48 hours in clinical situations in which the probability of sepsis is low. The purpose of this clinical report is to provide a practical and, when possible, evidence-based approach to the management of infants with suspected or proven early-onset sepsis. **PATHOGENESIS AND EPIDEMIOLOGY OF EARLY-ONSET SEPSIS**Before birth, the fetus optimally is maintained in a sterile environment.Organisms causing early-onset sepsis ascend from the birth canal eitherwhen the amniotic membranes ruptureor leak before or during the course oflabor, resulting in intra-amniotic infection.2 Commonly referred to as “chorioamnionitis,”intra-amniotic infectionindicates infection of the amniotic fluid,membranes, placenta, and/or deciduas. **Chorioamnionitis** is a major risk factor for neonatal sepsis. Sepsis can begin in utero when the fetus inhales or swallows infected amniotic fluid. The neonate can also develop sepsis in the hours or days after birth when colonized skin or mucosal surfaces are compromised. When defining intra-amniotic infection (chorioamnionitis) for clinical research studies, the diagnosis is typically based on the presence of maternal fever of greater than 38°C (100.4°F) and at least two of the following criteria: maternal leukocytosis (greater than 15 000 cells/mm3), maternal tachycardia (greater than 100 beats/minute), fetal tachycardia (greater than 160 beats/minute), uterine tenderness, and/or foul odor of the amniotic fluid. These thresholds are associated with higher rates of neonatal and maternal morbidity. Although fever is common in women who receive epidural anesthesia (15%–20%), histologic evidence of acute chorioamnionitis is very common in women who become febrile after an epidural (70.6%).3 Furthermore, most of these women with histologicchorioamnionitis do not have a positive placental culture (2011). The incidence of clinical chorioamnionitis varies	**5.FROM THE AMERICAN ACADEMY OF PEDIATRICS, CLINICAL REPORT Management of Neonates With Suspected or Proven Early-Onset Bacterial Sepsis** Polin RA, and the COMMITTEE ON FETUS AND NEWBORN **(COFN)** PEDIATRICS Volume 129, Number 5, May **2012**

inversely with gestational age. In the National Institute of Child Health and Human Development Neonatal Research Network, 14% to 28% of women delivering preterm infants at 22 through 28 weeks' gestation exhibited signs compatible with chorio-amnionitis (2010). The major risk factors for chorioamnionitis include low parity, spontaneous labor, longer length of labor and membrane rupture, multiple digital vaginal examinations (especially with ruptured membranes), meconium-stained amniotic fluid, internal fetal or uterine monitoring, and presence of genital tract microorganisms (eg, Mycoplasma hominis) 2010. In women with preterm labor and intact membranes, the rate of microbial invasion of the amniotic cavity is 32%, and if there is preterm premature rupture of membranes (PPROM), the rate may be as high as 75%. Many of the pathogens recovered from amniotic fluid in women with preterm labor or PPROM (eg, Ureaplasma species or mycoplasma species) do not cause early-onset sepsis (2008,2008, 2010).However, both Ureaplasma and Mycoplasma organisms can be recovered from the bloodstream of infants whose birth weight is less than 1500 g.11 When a pathogen (eg, GBS) is recovered from amniotic fluid, the attack rate of neonatal sepsis can be as high as 20%. The major risk factors for early-onset neonatal sepsis are preterm birth, maternal colonization with GBS, rupture of membranes >18 hours, and maternal signs or symptoms of intra-amniotic infection (2000,2006, 1999). Other variables include ethnicity (ie, black women are at higher risk of being colonized with GBS), low socioeconomic status, male sex, and low Apgar scores. Preterm birth/low birth weight is the risk factor most closely associated with early-onset sepsis (2011). Infant birth weight is inversely related to risk of early-onset sepsis.The increased risk of early-onset sepsisin preterm infants is also related tocomplications of labor and deliveryand immaturity of innate and adaptiveimmunity (2010).

DIAGNOSTIC TESTING FOR SEPSIS The clinical diagnosis of sepsis in the neonate is difficult, because many of the signs of sepsis are nonspecific and are observed with other non-infectious conditions. Although a normal physical examination is evidence that sepsis is not present,19,20 bacteremia can occur in the absence of clinical signs (2003). Available diagnostic testing is not helpful in deciding which neonate requires empirical antimicrobial therapy but can assist with the decision to discontinue treatment.

Blood Culture A single blood culture in a sufficient volume is required for all neonates with suspected sepsis. Data suggest that 1.0 mL of blood should be the minimum volume drawn for culture when a single pediatric blood culture bottle is used. Although 0.5 mL of blood has previously been considered acceptable, in vitro data from Schelonka et al demonstrated that 0.5 mL would not reliably detect low-level bacteremia (4 colony-forming units [CFU]/mL or less).23 Furthermore, up to 25% of infants with sepsis have low colony count bacteremia (≤4 CFU/mL), and two-thirds of infants younger than 2 months of age have colony counts <10 CFU/mL. A blood culture obtained through an umbilical artery catheter shortly after placement for other clinical indications is an acceptable alternative to a culture drawn from a peripheral vein. The risk of recovering a contaminant is greater with

a blood culture drawn from an umbilical vein. There are, however, data to suggest that a blood culture drawn from the umbilical vein at the time of delivery using a doubly clamped and adequately prepared segment of the cord is a reliable alternative to a culture obtained peripherally.

Tracheal Aspirates Cultures and Gram stains of tracheal aspirate specimens may be of value if obtained immediately after endotracheal tube placement.

Peripheral White Blood Cell Countand Differential Count Total white blood cell counts have littlevalue in the diagnosis of early-onsetsepsis and have a poor positive predictiveaccuracy.56,57 Many investigatorshave analyzed subcomponentsof the white blood cell count (neutrophilindices)—absolute neutrophil count,absolute band count, and immature tototal neutrophil (I/T)ratio—to identifyinfected infants. Like most diagnostictests for neonatal sepsis, neutrophil indiceshave proven most useful for excludinginfants without infection ratherthan identifying infected N Neonates. Neutropeniamay be a better marker forneonatal sepsis and has better specificitythan an elevated neutrophil count,because few conditions besides sepsis(maternal pregnancy-induced hypertension,asphyxia, and hemolytic disease)depress the neutrophil count ofneonates.

Platelet Counts Despite the frequency of low platelet counts in infected infants, they are a nonspecific, insensitive, and late indicator of sepsis 2009,2009). Moreover, platelet counts are not useful to follow clinical response to antimicrobial agents, because they often remain depressed for days to weeks after a sepsis episode.

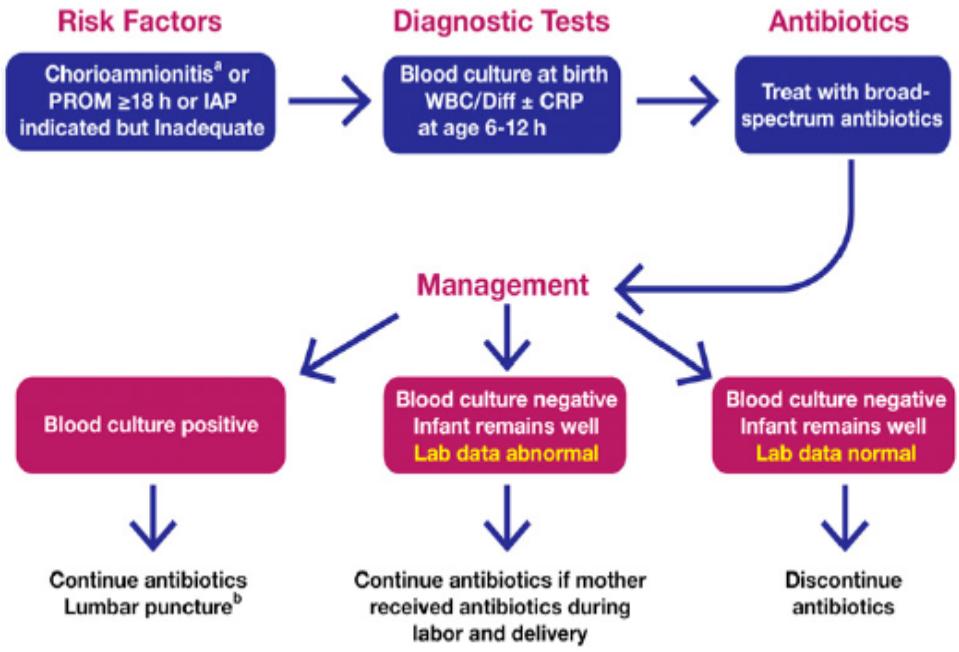
Acute –Phase reactants However, only C-reactive protein (CRP) and procalcitonin concentrations have been investigated in sufficiently large studies (2011,2010). CRP concentration increases within 6 to 8 hours of an infectious episode in neonates and peaks at 24 hours. The sensitivity of a CRP determination is low at birth, because it requires an inflammatory response (with release of interleukin-6) to increase CRP concentrations. The sensitivity improves dramatically if the first determination is made 6 to 12 hours after birth. Benitz et al have demonstrated that excluding a value at birth, 2 normal CRP determinations (8–24 hours after birth and 24 hours later) have a negative predictive accuracy of 99.7% and a negative likelihood ratio of 0.15 for proven neonatal sepsis. If CRP determinations remain persistently normal, it is strong evidence that bacterial sepsis is unlikely, and antimicrobial agents can be safely discontinued. Data are insufficient to recommend following sequential CRP concentrations to determine the duration of antimicrobial therapy in an infant with an elevated value (≥1.0 mg/dL). **Procalcitonin concentrations** increase within 2 hours of an infectious episode, peak at 12 hours, and normalize within 2 to 3 days in healthy adult volunteers. A physiologic increase in procalcitonin concentration occurs within the first 24 hours of birth, and an increase in serum concentrations can occur with noninfectious conditions (eg, respiratory distress syndrome). Procalcitonin concentration has a modestly better sensitivity than does CRP concentration but is less

specific.**TREATMENT OF INFANTS WITHSUSPECTED EARLY-ONSET SEPSIS**In the United States, the most commonpathogens responsible for early-onsetneonatal sepsis are GBS and Escherichiacoli.A combination of ampicillin andan aminoglycoside (usually gentamicin)is generally used as initial therapy, andthis combination of antimicrobial agentsalso has synergistic activity againstGBS and Listeria monocytogenes.Third-generation cephalosporins (eg,cefotaxime) represent a reasonable alternativeto an aminoglycoside. However,several studies have reported rapiddevelopment of resistance when cefotaximehas been used routinely for thetreatment of early-onset neonatal sepsis,and extensive/prolonged use ofthird-generation cephalosporins is a riskfactor for invasive candidiasis. Becauseof its excellent CSF penetration,empirical or therapeutic use of cefotaximeshould be restricted for use ininfants with meningitis attributable toGram-negative organisms.

In a retrospective study by Cordero and Ayers, the average duration of treatment in 695 infants (<1000 g) with negative blood cultures was 5 ± 3 days (2003). Cotten et al 2009, have suggested an association with prolonged administration of antimicrobial agents (>5 days) in infants with suspected early-onset sepsis (and negative blood cultures) with death and necrotizing enterocolitis. Two recent papers also support this association (Alexander et al 2011, Kuppala et al 2011).

PREVENTION STRATEGIES FOR EARLY-ONSET SEPSIS The only intervention proven to decrease the incidence of early-onset neonatal sepsis is maternal treatment with intrapartum intravenous antimicrobial agents for the prevention of GBS infections**. Adequate prophylaxis is defined as penicillin (the preferred agent), ampicillin, or cefazolin given for ≥4 hours before delivery. Erythromycin is no longer recommended for prophylaxis because of high resistance rates. In parturients who have a nonserious penicillin allergy, cefazolin is the drug of choice. For parturients with a history of serious penicillin allergy (anaphylaxis, angioedema, respiratory compromise, or urticaria), clindamycin is an acceptable alternative agent, but only if the woman's rectovaginal GBS screening isolate has been tested and documented to be susceptible. If the clindamycin susceptibility is unknown or the GBS isolate is resistant to clindamycin, vancomycin is an alternative agent for prophylaxis.**However, neither clindamycin nor vancomycin has been evaluated for efficacy in preventing early-onset GBS sepsis in neonates.**Intrapartum antimicrobial agents are indicated for the following situations:** 1. Positive antenatal cultures or molecular test at admission for GBS (except for women who have a caesarean delivery without labor or membrane rupture) 2. Unknown maternal colonization statuswith gestation <37 weeks, rupture of membranes >18 hours, or temperature >100.4°F (>38°C) 3. GBS bacteriuria during the current pregnancy 4. Previous infant with invasive GBS disease.

The greatest risk of early-onset sepsis occurs in infants born to women with chorioamnionitis who are also colonized with GBS and did not receive

intrapartum antimicrobial agents.  **FIGURE 1** Evaluation of asymptomatic infants <37 weeks' gestation with risk factors for sepsis. [a]The diagnosis of chorioamnionitis is problematic and has important implications for the management of the newborn infant. Therefore, pediatric providers are encouraged to speak with their obstetrical colleagues whenever the diagnosis is made. [b]Lumbar puncture is indicated in any infant with a positive blood culture or in whom sepsis is highly suspected on the basis of clinical signs, response to treatment, and laboratory results. IAP, intrapartum antimicrobial prophylaxis; WBC, white blood cell; Diff, differential white blood cell count.	
Abstract: There have been significant reductions in early-onset neonatal group B streptococcus (GBS) disease following implementation of maternal intrapartum antibiotic prophylaxis (IAP) policies. Nevertheless, GBS remains a leading cause of neonatal sepsis in Australia and New Zealand resulting in considerable morbidity and mortality, particularly among preterm infants.In the United States, the universal screening-based approach for identifying women for IAP results in apparently lower rates of early-onset neonatal GBS infection than risk-based assessment. In addition, IAP has altered the profile of newborn infants who develop early-onset disease. Many affected infants lack the typical intrapartum risk factors for GBS infection, are born to mothers with a negative GBS screen or represent missed opportunities for prevention. Clinicians should remain alert for signs of sepsis in any newborn infant. **We provide an update of GBS preventative management strategies in the perinatal period taking into account recent United States, Australian and New Zealand guidelines.** **Risk factors for early-onset neonatal GBS disease include**maternal GBS carriage (especially with heavy colonisation),previous infant with GBS disease, maternal fever, prolongedrupture of membranes, preterm delivery and low maternallevels of anti-capsular polysaccharide antibody to the colonisingGBS serotype (2002, 2008).Preterm infants are at significantly higher(3–30-fold) risk of GBS disease and have worse outcomes thanthose	**6. Review article** **Prevention of neonatal group B streptococcus disease in the 21st century** Clifford V, Garland SM, Grimwood K. Journal of Paediatrics and Child Health, **2011**

born at term.9 Nonetheless, although prematurity is a riskfactor for GBS disease, more than 70% of GBS disease occurs interm infants (2008).

Early-onset neonatal GBS disease usually presents within thefirst 24 h of life with either sepsis or pneumonia (1995,2002,2004).Clinicaldeterioration is often rapid and includes respiratory distress,temperature instability, circulatory impairment and apnoea.Nevertheless, **mortalityrates still remain high in preterm babies and can exceed10% in those born before 33 weeks gestation** (2009,2004).

Primary prevention: Maternal IAP 1.Universal screening strategy that requires all pregnant women to have recto-vaginal swabs taken for GBS culture at35–37 weeks gestation. If taken within 5 weeks of delivery, culture results have positive and negative predictive values of 77–87% and 94–96% respectively for GBS in the birth canal during labour (2005,1996). 2.Risk-based assessment, which is non-culture based and requires intrapartum maternal fever ≥38°C or membrane rupture ≥18 h to be present before offering IAP. Both strategies also recommend IAP for women presenting with preterm labour (<37 weeks gestation and no GBS cultures performed within the previous 5 weeks), GBS bacteriuria ($\geq 10^4$ colony-forming units/mL) detected anytime during the current pregnancy or a GBS-infected infant previously. Implementation of both GBS prevention strategies has contributed to a 65–82% decline in early-onset GBS neonatal disease in the United States, Australia and New Zealand (2004,2000).A concomitant 21% decline in serious maternal post-partum GBS infections in the United States from 0.29 to 0.23 per 1000 live births was also observed (Schrag et al 2003). More importantly, a large retrospective cohort study in the United States involving more than 600 000 live births found that the screening-based approach was at least 50% more effective than the risk-based strategy (0.33 vs. 0.59 per 1000 live births respectively) at preventing GBS disease in the first week of life (Schrag et al 2004). This led to the United States Centres for Disease Control (CDC) in 2002 (and again in 2010) to recommend the universal screening-based approach as its preferred GBS prevention strategy with risk-based assessment to be used only when GBS culture results were unavailable (Verani et al 2010).While Australian guidelines (2010) have largely followed United States policies, others including New Zealand, the United Kingdom and many European countries still recommend riskbased strategies (2010 Antibiotic Expert Group, Campbell et al 2004, Hughes et al 2003, Trijbels-Smeulders et al 2007).**Secondary prevention: Managing infants 'at risk' of GBS disease**

Any newborn infant with signs of sepsis (e.g. any combination of respiratory distress, apnoea, pallor with poor peripheral perfusion, fever ≥ 38°C or unstable temperature and acidosis) **should have a full diagnostic evaluation** (usually full blood examination, blood and cerebrospinal fluid cultures, and chest X-ray if indicated) **and receive broad-spectrum antibiotics (e.g. penicillin and gentamicin) while awaiting the results of cultures** (Verani et al 2010,Vergnano et al 2011,Campbell 2004). It is worth emphasising that clinical signs are highly sensitive indicators of sepsis

(Escobar et al 2000).

Maternal chorioamnionitis indicates a high risk for earlyonset neonatal GBS disease, even when the mother has received appropriate intrapartum antibiotics (Escobar et al 2000). While the CDC guidelines recommend that all well-appearing babies born to mothers with suspected chorioamnionitis should undergo a limited diagnostic evaluation and receive antibiotics while awaiting the results of cultures (Verani et al 2010), **the New Zealand consensus guidelines advise just close observation and that investigations and treatment are only required if the neonate shows signs of sepsis** (Campbell 2004) (Fig. 2)

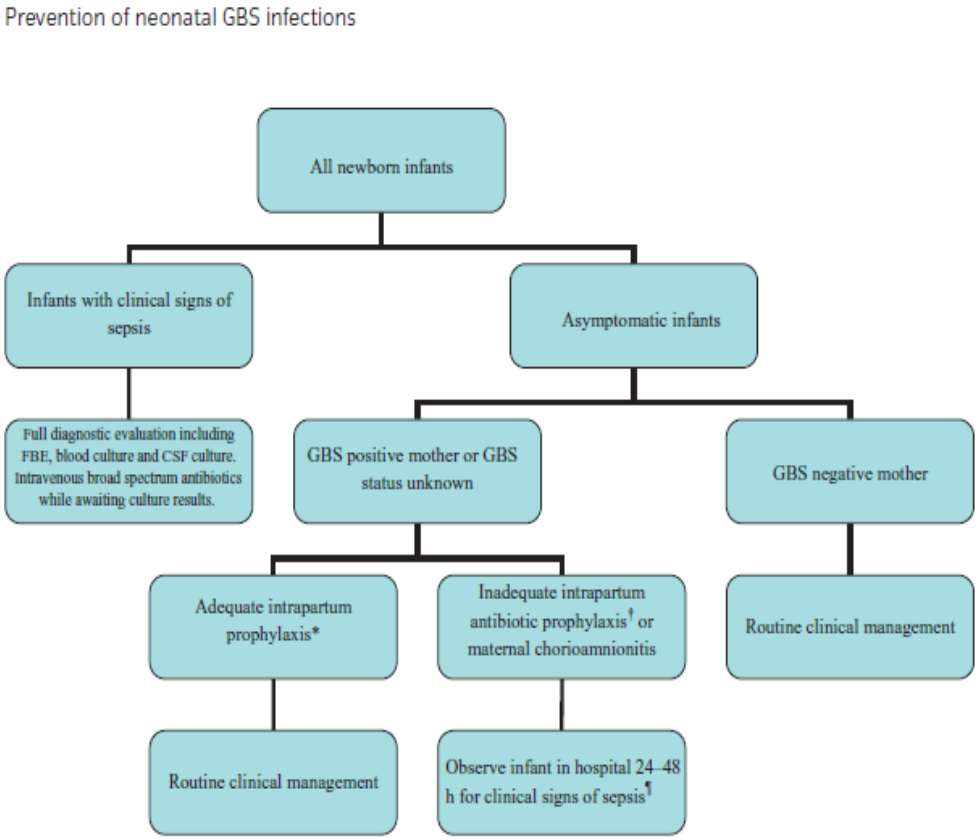


Fig. 2 Neonatal management algorithm (adapted from Campbell *et al.*[27]). *Adequate prophylaxis consists preferably of penicillin (or ampicillin) ≥4 h prior to delivery in the presence of any factors identified in Figure 1. †Inadequate prophylaxis = no prophylaxis or antibiotics administered <4 h prior to delivery or an antibiotic other than penicillin or ampicillin administered (e.g. in case of maternal penicillin allergy). ¶If clinical signs of sepsis appear, manage as per 'clinical sepsis' section of algorithm. CSF, cerebrospinal fluid; FBE, full blood examination; GBS, group B streptococcus.

Since publication of the initial guidelines for the prevention of group B streptococcal disease in 1996, the incidence of perinatal infection has decreased significantly. Intrapartum antibiotic prophylaxis together with appropriate management of neonates at increased risk for early-onset sepsis not only reduces morbidity and mortality, but also decreases the burden of unnecessary or prolonged antibiotic therapy. This article provides healthcare workers in Switzerland with evidence-based and best-practice derived guidelines for the assessment and management of term and late preterm infants (>34 weeks) at increased risk for perinatal bacterial infection.
Management of neonates at increased risk for early-onset sepsis depends on clinical presentation and risk factors.Asymptomatic infants with risk factors for early-onset sepsis should be observed closely in an inpatient setting for the first 48 hours of life. Symptomatic neonates must be treated promptly with intravenous antibiotics. As clinical and laboratory signs of neonatal infectionare nonspecific, it is mandatory to reevaluate the need forcontinued antibiotic therapy after 48 hours.

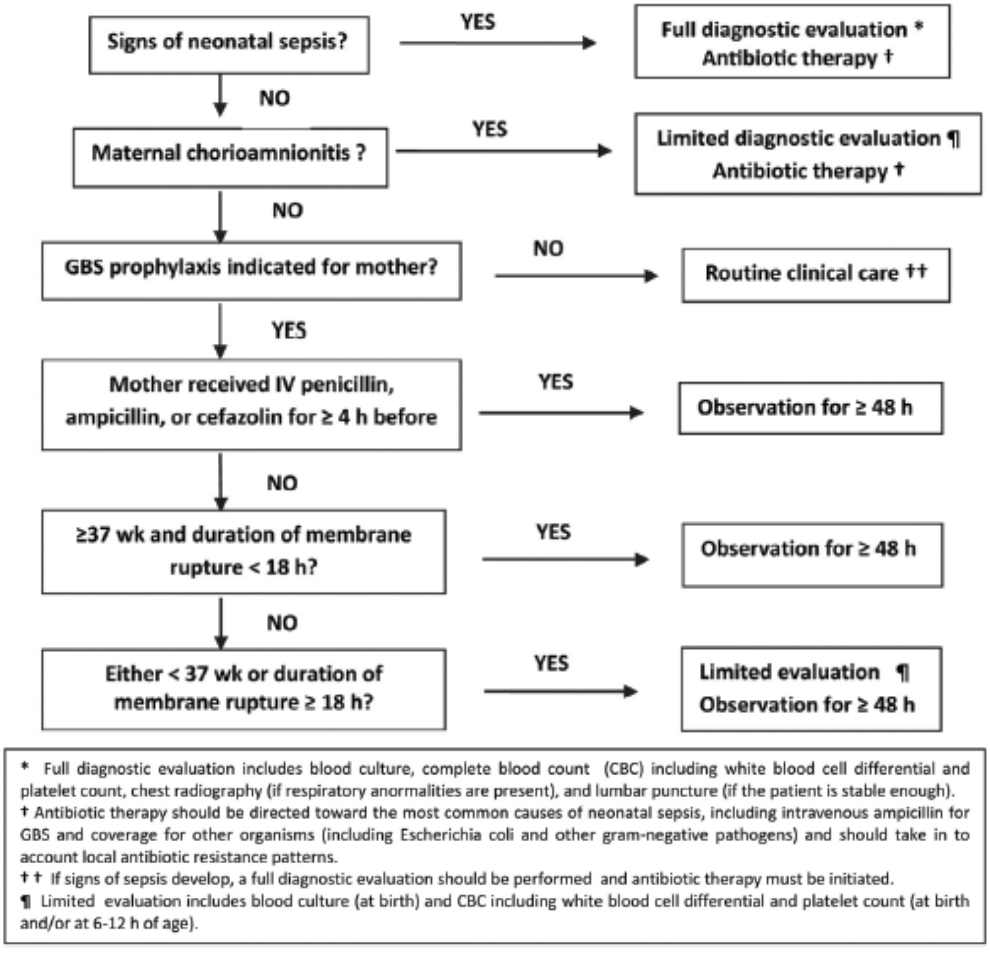
Figure 1

Management of term and late preterm infants (>34 weeks) at increased risk for neonatal bacterial infection (early-onset sepsis).
(1.) Tachypnoea, respiratory distress, apnoea, tachycardia/ bradycardia, poor peripheral perfusion, mottling, temperature instability, lethargy, irritability, changes in tone, vomiting, poor feeding.
(2.) Maternal group B streptococcus (GBS) colonisation (vaginal/ rectal swab: current or previous, bacteruria), preterm birth, prolonged rupture of membranes >18 hours, chorioamnionitis (maternal fever >38 °C plus two further symptoms: maternal leucocytosis, foetal tachycardia, painful or tender uterus, fetid amniotic fluid), required intrapartum prophylaxis missing or inadequate.
(3.) Monitor vital signs every 4 hours: respiration, temperature, peripheral perfusion, colour.
(4.) Elective Caesarean section (no rupture of membranes or contractions): no postnatal observation of baby necessary (regardless of maternal GBS status).
(5.) If there are coexisting risk factors and/or the baby has clinical signs, discuss indication for laboratory tests with responsible neonatologist.

Contrary to the revised CDC recommendations, we do not recommend empirical antibiotic therapy for asymptomatic neonates whose mothers have signs of chorioamnionitis. We recommend close observation for the first 48 hours, as for asymptomatic neonates with other risk factors for infection. This management is
in agreement with the recent recommendations from Australia and New Zealand as well as the AAP 2012 guidelines for the management of neonates at increased risk for earlyonset sepsis. The risk of neonatal infection increases with the number of coexisting risk factors and is highest for term infants of GBS positive mothers with chorioamnionitis.
Antibiotic therapy for suspected neonatal infection An aminoglycoside (amikacin or gentamicin) combined with amoxicillin given intravenously is the standard empiric therapy. Appropriate doses for neonates within the first week of life are: gentamicin 4–5 mg/kg/dose or amikacin 15 mg/kg/dose

7.Recommendations for term and late preterm infants at risk for perinatal bacterial infection
Revised guidelines of the Swiss Society of Neonatology in collaboration with thePaediatric Infectious Disease Group of Switzerland (PIGS): modified versionbased on a previous Publication in the Journal of the Swiss Society of Paediatrics [1]*
Stocker M, Berger C, McDougall J, Giannoni E Taskforce for the Swiss Society of Neonatology and the Paediatric Infectious Disease Group of Switzerland

Review article, September **2013**, doi:10.4414/smw.2013.13873
Cite this as: Swiss Med Wkly.**2013;**143:w13873

intravenously every 24 hours and amoxicillin 50–100 mg/kg/dose intravenously every 12 hours. There is a need for therapeutic drug monitoring for aminoglycoside therapy. Cephalosporins should be avoided as first-line therapy because of the high risk of developing resistance and should be restricted to special cases.	
Abstract The incidence of neonatal early-onset group B streptococcus (GBS EOS) sepsis has declined during the last decade since the implementation of intrapartum antibiotic prophylaxis endorsed by Centers for Disease Control and Prevention (CDC) guidelines. All the CDC guidelines versions provide recommendations for neonatal management. The neonatal algorithm of CDC has not been universally accepted and hence different algorithms have been suggested. Since all approaches to disease prevention are still imperfect, an optimal algorithm for GBS EOS prevention is still lacking; the development of improved diagnostic methods of distinguishing at-risk infants may contribute to improve the clinician's approach. The Queensland Maternity and Neonatal Clinical Guidelines Program in their guidelines for the prevention of GBS EOS, published in 2010, suggests the evaluation of asymptomatic infants aged ≥37 weeks and **also the implementation of empirical antibiotic therapy in those aged <37 weeks in case of inadequate IAP** [2010]. C. Tzialla et al. / Early Human Development 90S1 (2014) S35–S38  * Full diagnostic evaluation includes blood culture, complete blood count (CBC) including white blood cell differential and platelet count, chest radiography (if respiratory anormalities are present), and lumbar puncture (if the patient is stable enough). † Antibiotic therapy should be directed toward the most common causes of neonatal sepsis, including intravenous ampicillin for GBS and coverage for other organisms (including Escherichia coli and other gram-negative pathogens) and should take in to account local antibiotic resistance patterns. †† If signs of sepsis develop, a full diagnostic evaluation should be performed and antibiotic therapy must be initiated. ¶ Limited evaluation includes blood culture (at birth) and CBC including white blood cell differential and platelet count (at birth and/or at 6-12 h of age). **Fig. 1.** Algorithm for the prevention of early-onset GBS infection in the newborn, CDC 2010 [4].	**8.Review article** **Which is the optimal algorithm for the prevention of neonatal early-onset group B streptococcus sepsis?** Tzialla C, Borghesi A, Longo S, Stronati M. Early Human Development 90S1 **(2014)** S35–S38

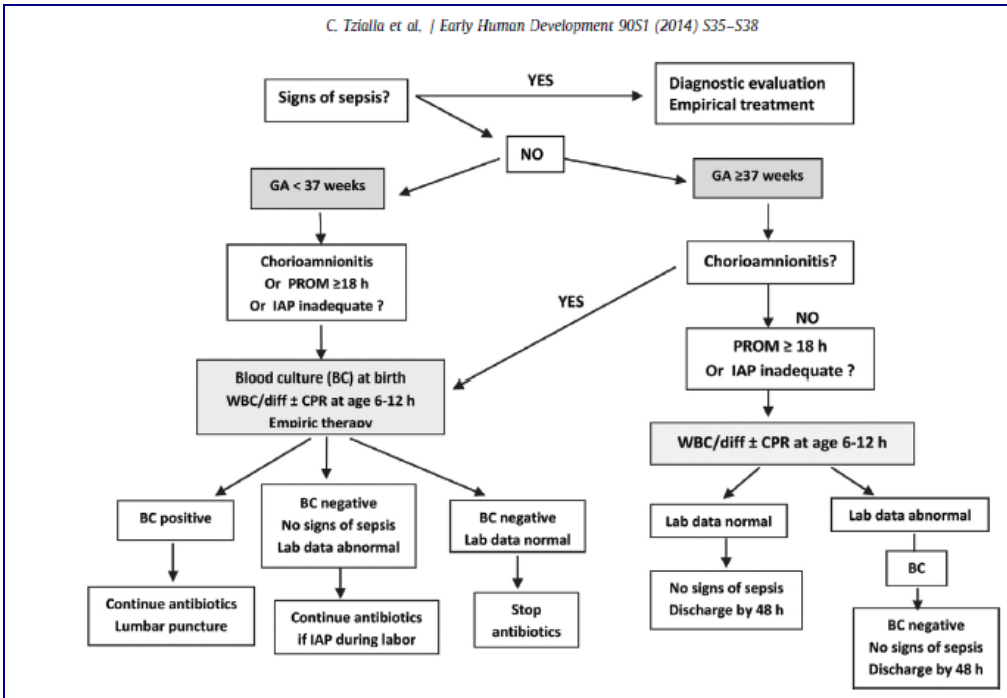


Fig. 2. Algorithm for management of healthy-appearing high-risk infants [10].

COFN algoritm 2012

Even the Committee on Fetus and Newborn (COFN) suggests a different algorithm for the management of healthy-appearing at-risk infants. This category includes infants with one of the following risk factors for sepsis: colonization with GBS if the mother hasn't received or received inadequate IAP, PROM >18 hours or maternal chorioamnionitis. According the authors the
decision of whether to treat an at-risk infant depends on the risk factors present and gestational age and the threshold for initiating empirical antimicrobial treatment generally decreases with increasing numbers of risk factors for infection and greater levels of prematurity [Polin, COFN 2012]. The neonatal algorithm suggested is shown in Fig. 2.

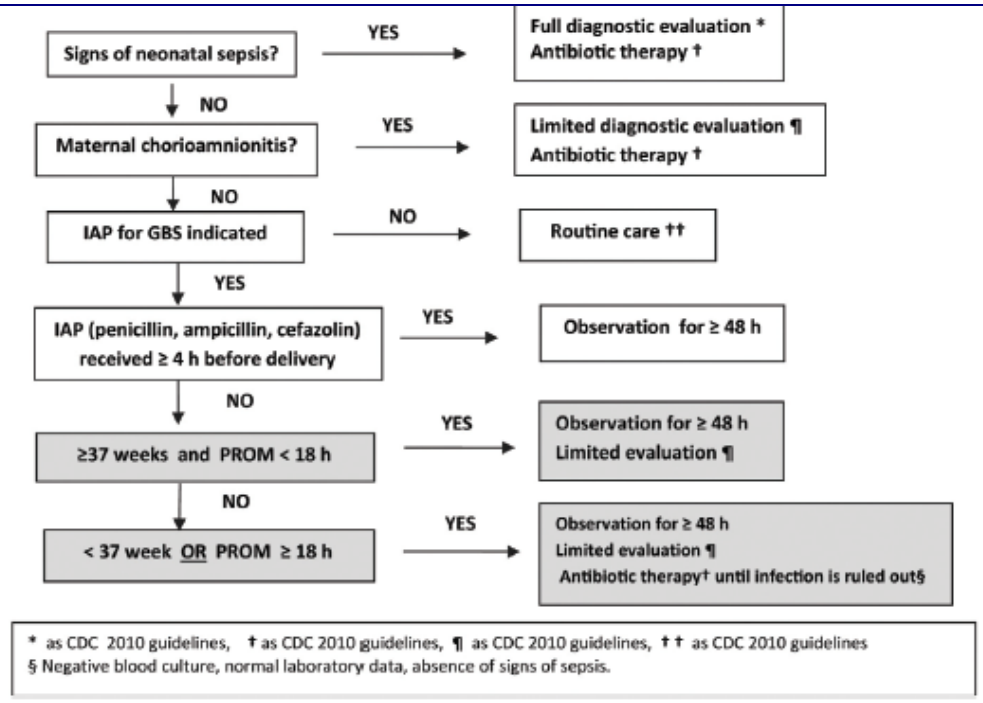


Fig. 3. Local algorithm for neonatal management.

According to the above algorithm, the asymptomatic infants with inadequate IAP aged ≥37 weeks with PROM <18 hours must undergo limited diagnostic evaluation, and those aged <37 weeks gestation or with PROM ≥18 hours must undergo diagnostic evaluation and empirical antibiotic treatment until infection is
ruled out (negative blood culture, normal laboratory data, absence of signs of sepsis).

Abstract The management of neonatal sepsis is challenging owing to complex developmental and environmental factors that contribute to inter-individual variability in the pharmacokinetics and pharmacodynamics of many antimicrobial
agents. In this review, we describe (i) the changing epidemiology of early- and late-onset neonatal sepsis; (ii) the pharmacologic considerations that influence the safety and efficacy of antibacterials, antifungals, and immunomodulatory
adjuvants; and (iii) **the recommended dosing regimens for pharmacologic agents commonly used in the treatment and prevention of neonatal sepsis**. Neonatal sepsis is marked by highmorbidity andmortality, such that prompt initiation ofantimicrobial therapy is essential following culture collection. **Before culture results are available, combination therapy with ampicillin and an aminoglycoside is recommended**. When **meningitis is suspected, ampicillin and cefotaxime may be considered.** Following identification of the causative organism and in vitro susceptibility testing, antimicrobial therapy may be narrowed to provide targeted coverage. **Therapeutic drug monitoring should be considered for neonates receiving vancomycin or aminoglycoside therapies.** For neonates with invasive fungal infections, the development of newantifungal agents has significantly improved therapeutic outcomes in recent years. Liposomal amphotericin B has been found to be safe and efficacious in patients with renal impairment ortoxicity caused by conventional amphotericin B.

9.Review article Considerations in the Pharmacologic Treatment and Prevention of Neonatal Sepsis

Stockmann C, Spigarelli MG, Campbell SC, Constance JE, Courter JD, Thorell EA, Olson J, Sherwin C.M. T.

Pediatr Drugs **(2014)** 16:67–81

Antifungal prophylaxis with fluconazole has also been reported to dramatically reduce rates of neonatal invasive fungal infections and to improve long-term neurodevelopmental outcomes among treated children. **Additionally, several large multicenterstudies are currently investigating the safety and efficacy of oral lactoferrin as an immunoprophylactic agent for the prevention of neonatal sepsis.**

Table 1 Distribution of common early- and late-onset neonatal sepsis pathogens

Most commonly isolated (???), frequently isolated (??), occasionally isolated (?),
rarely isolated (-). Adapted from Edwards et al. [2011]

Etiological agents	Early-onset (<7 days of life)	Late-onset (≥7 days of life)
Gram-positive bacteria		
Coagulase-negative staphylococci	–	+++
Enterococcus species	+	++
Group B streptococcus	+++	+
Listeria monocytogenes	+	+
Staphylococcus aureus	+	+++
Streptococcus pneumoniae	+	+
Viridans streptococci	+	+
Gram-negative bacteria		
Citrobacter species	–	+
Enterobacter species	+	++
Escherichia coli	+++	++
Haemophilus influenzae	+	–
Klebsiella species	+	++
Neisseria meningitidis	–	+
Pseudomonas species	–	+
Salmonella species	–	+
Serratia marcescens	–	+
Anaerobic bacteria		
Bacteroides species	+	+
Clostridium species	–	+
Fungi		
Candida albicans	+	+
Candida parapsilosis	–	+

Table 3 Antibiotic dosing and monitoring recommendations for the treatment of neonatal sepsis

Antibiotic	Route	Age	Dosing recommendations	
Gentamicin	IV, IM	PNA ≤ 7 days	Weight < 2 kg	5 mg/kg/dose every 48 h
			Weight ≥ 2 kg	4 mg/kg/dose every 24 h
		PNA > 7 days	Weight < 2 kg	4–5 mg/kg/dose every 24–48 h
			Weight ≥ 2 kg	4 mg/kg/dose every 12–24 h
Ampicillin[a]	IV, IM	PNA ≤ 7 days	Weight < 2 kg	50 mg/kg/dose every 12 h
			Weight ≥ 2 kg	50 mg/kg/dose every 8 h
		PNA > 7 days	Weight < 2 kg	50 mg/kg/dose every 8 h
			Weight ≥ 2 kg	50 mg/kg/dose every 6 h
Cefotaxime[a]	IV, IM	PNA ≤ 7 days	Weight < 2 kg	50 mg/kg/dose every 12 h
			Weight ≥ 2 kg	50 mg/kg/dose every 12 h
		PNA > 7 days	Weight < 2 kg	50 mg/kg/dose every 8–12 h
			Weight ≥ 2 kg	50 mg/kg/dose every 8 h
Linezolid	IV	PNA ≤ 7 days	Weight < 2 kg	10 mg/kg/dose every 12 h
			Weight ≥ 2 kg	10 mg/kg/dose every 8 h
		PNA > 7 days	Weight < 2 kg	10 mg/kg/dose every 8 h
			Weight ≥ 2 kg	10 mg/kg/dose every 8 h

Vancomycin	IV	GA ≤ 28 weeks	SCr < 0.9 mg/dL	15 mg/kg/dose every 12 h
			SCr 0.9–1.1 mg/dL	20 mg/kg/dose every 24 h
			SCr 1.2–1.4 mg/dL	15 mg/kg/dose every 24 h
			SCr 1.5–1.8 mg/dL	10 mg/kg/dose every 24 h
			SCr > 1.8 mg/dL	15 mg/kg/dose every 48 h
		GA > 28 weeks	SCr < 0.7 mg/dL	15 mg/kg/dose every 12 h
			SCr 0.7–0.9 mg/dL	20 mg/kg/dose every 24 h
			SCr 1.0–1.2 mg/dL	15 mg/kg/dose every 24 h
			SCr 1.3–1.6 mg/dL	10 mg/kg/dose every 24 h
			SCr > 1.6 mg/dL	15 mg/kg/dose every 48 h

Dosing recommendations were obtained from the American Academy of Pediatrics' Red Book [56]

GA gestational age, *IM* intramuscular, *IV* intravenous, *PNA* postnatal age, *SCr* serum creatinine

[a] Higher dosages are recommended for the treatment of meningitis [56]

Red Book 2012

Table 5 Antifungal dosing and monitoring recommendations for the treatment of neonatal sepsis

Antifungal	Route	Age	Dosing recommendations	
Amphotericin B	IV	–	–	0.5 mg/kg/dose every 24 h
Liposomal amphotericin B	IV	–	–	3–5 mg/kg/dose every 24 h
5-Fluorocytosine	PO	PNA ≤ 7 days	Weight ≤ 2 kg	75 mg/kg/day every 8 h
			Weight > 2 kg	75 mg/kg/day every 6 h
		PNA > 7 days	Weight ≤ 2 kg	75 mg/kg/day every 6 h
			Weight > 2 kg	75 mg/kg/day every 6 h
Fluconazole	IV, PO	–	Loading dose	25 mg/kg
		–	Maintenance dose	12 mg/kg/dose every 24 h
Caspofungin	IV	–	–	25 mg/m^2/dose every 24 h
Micafungin	IV	–	–	2 mg/kg/dose every 24 h[a]
			Weight < 1 kg	10 mg/kg/dose every 24 h[b]
			Weight ≥ 1 kg	7–10 mg/kg/dose every 24 h[b]

Dosing recommendations were obtained from the American Academy of Pediatrics' Red Book [56]

IV intravenous, *PNA* postnatal age, *PO* oral

[a] Dosing recommendations for the treatment of candidemia and invasive candidiasis

[b] Dosing recommendations for the treatment of disseminated candidiasis

Abstract

Background: Although neonatal infections cause a significant proportion of deaths in the first week of life, little is known about the burden of neonatal disease originating from maternal infection or colonization globally. This paper describes the prevalence of vertical transmission – the percentage of newborns with neonatal infection among newborns exposed to maternal infection.

Methods: We searched Pubmed, Embase, Scopus, Web of Science, Cochrane Library, and WHO Regional Databases for studies of maternal infection, vertical transmission, and neonatal infection. Studies that measured prevalence of
bacterial vertical transmission were included. Random effects meta-analyses were used to pool data to calculate prevalence estimates of vertical transmission.

Results: 122 studies met the inclusion criteria. Only seven studies (5.7%) were from very high neonatal mortality settings. Considerable heterogeneity existed between studies given the various definitions of infection (lab-confirmed,
clinical signs), colonization, and risk factors of infection. The prevalence of early onset neonatal lab-confirmed infection among newborns of mothers with lab-confirmed infection was 17.2% (95%CI 6.5-27.9). The prevalence

10.Prevalence of early-onset neonatal infection among newborns of mothers with bacterial infection or colonization: a systematic review and meta-analysis

Chan GJ, Lee ACC, Baqui AH, Tan J, Black RE.

BMC Infectious Diseases **(2015)** 15:118

of neonatal lab-confirmed infection among newborns of colonized mothers was 0% (95% CI 0.0-0.0). The prevalence of neonatal surface colonization among newborns of colonized mothers ranged from 30.9-45.5% depending on the organism. The prevalence of neonatal lab-confirmed infection among newborns of mothers with risk factors (premature rupture of membranes, preterm premature rupture of membranes, prolonged rupture of membranes) ranged from 2.9-19.2% depending on the risk factor. **Conclusions:** The prevalence of early-onset neonatal infection is high among newborns of mothers with infection or risk factors for infection. More high quality studies are needed particularly in high neonatal mortality settings to accurately estimate the prevalence of early-onset infection among newborns at risk.	
Epidemiologic evidence of higher mortality and morbidity among premature neonates with sterile cultures and long empirical antibiotic courses has recently emerged, and concerns over rising antimicrobial resistance among common pathogens, including E. coli, with two thirds of isolates from EOS E. coli samples ampicillin resistant, have grown.[Weston et al 2011, Stoll et al 2011, Cotten 2009, Bizzarro et al 2008, Kuppala et al 2011]. **Abstract** **Purpose of review**—Clinicians' adherence to AAP and CDC Guidelines to prevent Group B Streptococcal (GBS) early onset sepsis (EOS) have reduced GBS EOS. While evidence-based testing and empirical antibiotic initiation is likely saving lives, clinicians have less compelling data to guide duration of empirically initiated antibiotics when cultures remain sterile and clinical signs resolve quickly. Our purpose is to review current opinions and evidence influencingclinicians' choices for duration of empirically initiated antibiotics in newborns with sterile cultures. **Recent findings**—Retrospective cohort studies indicate potential for harm with longer duration of empirical antibiotics for EOS when cultures are sterile. Cohort studies indicate timing of widely used tests used to estimate EOS risk affects their predictive value, and tests acquired 24 – 48 hours postnatally may provide reassurance for safe discontinuation. **Summary**—Every day clinicians caring for thousands of neonates in the US stop antibiotics which were started empirically to treat EOS on the first postnatal day. **Evidence is lacking to support a universal approach to decisions on duration of empirical antibiotics when cultures remain sterile.** Reviewing predictive value relative to timing of laboratory testing can help clinicians develop locally appropriate antimicrobial duration decision-making guidelines. **Conclusion** We acknowledge the limitations in the evidence to guide decisions regarding duration of empirical antibiotics for EOS for every situation. We also acknowledge that clinicians have to make these decisions daily, and we offer suggestions for approaches to term and near term neonates who were started on empirical antibiotics to treat EOS, and whose cultures are sterile at 48 postnatal hours.	**11. Review article** **Duration of empirical antibiotic therapy for infants suspected of early-onset sepsis** Cotten MC, Smith PB. Curr Opin Pediatr. **2013** April ; 25(2): 167–171.

Term/late preterm neonate on empirical antibiotics for EOS plus sterile cultures at 48 postnatal hours and: **1.** Clinical signs of infection that persisted over 24 hours: 7 days **2.** Clinical signs initially absent, but became apparent after first postnatal hour and persisted more than 24 hours: 7 days **3.** Labs drawn for risk factors, clinical signs absent, initial (4 postnatal hours) laboratory CBC normal: 48 hours **4.** Labs drawn for risk factors, clinical signs transient (resolved by 8 hours), initial CBC abnormal: obtain CRP at 24 and 48 hours. If CRPs are low, clinical exam stays normal, stop antibiotics at 48 hours.	
Abstract **Objective:** The objective of this randomized controlled trial was to compare the treatment failure of suspectedbearly onset neonatal sepsis with either 3-day or 5-day course of empirical antibiotic therapy. **Methods:** Infants with birth weight over 1500 g and/or gestational age over 34 weeks within 7 days postnatal age with clinical symptoms of neonatal sepsis received empirical antibiotics (Ampicillin + Amikacin) in two neonatal intensive care units. After 72 hours if the result of blood culture was negative and symptoms resolved they were randomly allocated to 3-day or 5-day groups. The main outcome was treatment failure which was defined as reappearance of symptoms of sepsis within two weeks after discontinuation of antibiotics. Infants with congenital anomalies, localized infections, asphyxia, those undergoing surgery or when serum C-reactive protein levels remained abnormal despite treatment, were not included. Randomization was accomplished with simple randomization procedure. **Findings:** Sixty patients were randomized in a 1:1 ratio to either group. Baseline characteristics were similar between two groups. The follow-up period was 2 weeks with no lost to follow-up.One infant in 3-day group had treatment failure compared with no treatment failure in 5-day group (P=0.5). No serious harm was observed due to our empirical antibiotic regimen. **Conclusion:** The results of this study indicated no evidence that treatment failure differs between 3-day and 5-day course antibiotic therapy for suspected early onset uncomplicated neonatal sepsis in late preterm and term newborns.	**12.3-Day versus 5-Day Course of Intravenous Antibiotics for Suspected Early Onset Neonatal Sepsis: A Randomized Controlled Trial** Pasha YZ, Ahmadpour-Kacho M, Behmadi R, Jahangir T. *Iranian Journal of Pediatrics, Volume 24 (Number 6), December **2014**, Pages: 673-678*
Abstract **Objective** To investigate the outcomes following prolonged empirical antibiotic administration to premature infants in the first week of life, concluding subsequent late onset sepsis (LOS), necrotizing enterocolitis (NEC), and death. **Study design Retrospective cohort study** Study infants were ≤32 weeks gestational age and ≤ 1500 grams birth weight who survived free of sepsis and NEC for 7 days. Multivariable logistic regression was conducted to determine independent relationships between prolonged initial empirical antibiotic therapy (≥ 5 days) and study outcomes controlling for birth weight, gestational age, race,	**13.Prolonged Initial Empirical Antibiotic Treatment is Associated with Adverse Outcomes in Premature Infants** Kuppala VS, Meinzen-Derr J,

prolonged premature rupture of membranes, days on high frequency ventilation in 7 days, and the amount of breast milk received in the first 14 days of life. **Results** Of the 365 premature infants surviving 7 days free of sepsis or NEC, 36% received prolonged initial empirical antibiotics 8ampicillin and gentamicin), which was independently associated with subsequent outcomes: LOS (odds ratio [OR] 2.45, 95% confidence interval [CI] 1.28–4.67) and the combination of LOS, NEC, or death (OR 2.66, 95% CI 1.12–6.3). **Conclusions Prolonged administration of empirical antibiotics to premature infants with sterile cultures in the first week of life is associated with subsequent severe outcomes.** Judicious restriction of antibiotic use should be investigated as a strategy to reduce severe outcomes for premature infants.	Ardythe L, Morrow AL, Schibler KR. Pediatr. **2011** November ; 159(5): 720–725.
Summary The immature immune system of preterm neonates puts them at higher risk of neonatal sepsis. We conducted a part-blinded randomised controlled trial to compare the effect of routine antibiotic treatment on the incidence of clinical sepsis in pretermneonates. Preterm neonates without other risk factors for infection admitted in the first 12 h of life were randomised to receive routine antibiotics or to a control group (no antibiotics unless clinically indicated). The primary outcome variable was the incidence of clinical sepsis. Secondary outcomes were the incidence of positive blood cultures, necrotising enterocolitis (NEC) stage II or III, or death, and the duration of hospital stay. The incidence of clinical sepsis was comparable in both groups (intervention 31.9%, control 25.4%; P ¼ 0.392). Mortality was equivalent in both groups. The control group had significantly more positive blood cultures (P ¼ 0.002). The incidence of NEC and the duration of hospital stay were comparable in both groups. **In low risk preterm neonates we found no evidence that routine antibiotic use has a protective effect.**	**14.Routine antibiotic use in preterm neonates: a randomised controlled trial** Tagare A., Kadam S, Vaidya U., Pandit A. Journal of Hospital Infection **(2010)** 74, 332e336
Ampicillin (AMP) and penicillin G (PEN) in combinationwith gentamicin (GEN) are the most widely recommended andused regimens in the empiric treatment of neonatal EOS.1,8 Thetwo treatments differ in their antibacterial coverage, with AMPhaving greater efficacy against Gram-negative microorganismssuch as *Escherichia coli.* This distinction is likely most relevantin the treatment of ELBW neonates, because Gram-negative pathogens, particularly *E. coli*, have been found to be dominantamong EOS-causative microorganisms in this population (Ronnestad et al 2005, Klinger 2009, Lopez Sastre 2000, Stoll 2005). **Abstract *Background***: There are no comparative data on the impact of different empiric antibiotic regimens on early bowel colonization as well as on clinical efficacy in extremely low-birthweight (ELBW) neonates at risk of early onset sepsis (EOS). ***Methods***: A subgroup analysis was carried out of ELBW neonates recruited into a two-center, prospective, cluster randomized study comparing ampicillin and penicillin both combined with gentamicin, within the first 72 h of life. A composite primary end-point (need for change of antibiotics within 72 h and/or 7 day all-cause mortality) and the rate and duration of colonization by opportunistic aerobic microorganisms were assessed using hierarchical models corrected for study center and period.	**15.Ampicillin versus penicillin in the empiric therapy of extremely low-birthweight neonates at risk of early onset sepsis** Metsvaht T, Ilmoja M-L, Parm Ü, Merila M, Maipuu L, Müürsepp P, Julge K, Sepp E, Lutsar I. *Pediatrics International***(2011)** 53, 873–880

Results: In the ampicillin (*n* = 36) and penicillin (*n* = 39) groups change of antibiotics, 7 day mortality and the composite end-point occurred at similar rates. Neonatal intensive care unit mortality for infants with gestational age <26 weeks was lower in the ampicillin group. Ampicillin treatment was associated with a higher colonization rate by *Klebsiella pneumoniae*, including ampicillin-resistant strains. ***Conclusion***: Preliminary data indicate an urgent need for adequately powered studies of early antibiotic therapy in the subpopulation of ELBW neonates at risk of EOS.	
Although not evaluated in appropriately powered clinicaltrials, the combination of aminoglycoside and AMP or PENhas remained the treatment of choice for EOS in manynurseries world-wide (Mtitimila et al 2004, Clark et al 2006). Recent changes in the bacterialaetiology of EOS, with decreasing rates of group B streptococci(GBS) and increasing Escherichia coli raise the issueof potential differences between the two regimens. The predominanceof Gram-negative rods in bacterial aetiology ofEOS among preterm neonates, reported in Europe(Ronnestadet al 2005)andUnited States (Stoll et al 2005, Bizzarro et al 2008),as well as in Israel (Klinger et al 2009), suggests higherpotential efficacy of AMP at least in this subpopulation. **Abstract** **Aim**: We aimed to compare the clinical efficacy of ampicillin (AMP) vs. penicillin (PEN) both combined with gentamicin in the empirical treatment of neonates at risk of early onset neonatal sepsis (EOS). **Methods:** We performed an open label cluster randomized equivalence study in both Estonian neonatal intensive care units, including neonates with suspected EOS, aged less than 72 h. Primary end-point was clinical failure rate, expressed by need for change of antibiotic regimen within 72 h and/or 7-day all cause mortality. Bowel colonization was followed with biweekly perineal swab cultures. **Results:** Incidence of proven EOS was 4.9%. Among neonates receiving AMP (n = 142) or PEN (n = 141) change of antibiotic regimen within 72 h (10/142 vs. 10/141; OR 1.02; 95% CI 0.40–2.59), 7-day mortality (11/142 vs. 14/141; OR 0.76; 95% CI 0.33–1.75) and over-all treatment failure (20/142 vs. 20/141; OR 1.01; 95% CI 0.52–1.97) occurred at similar rates. The only differences in gut colonization were lower number of patients colonised with enterococci, S. Aureus and AMP resistant Acinetobacter spp. in AMP and lower number of those with S. haemolyticus and S. hominis in PEN arm. **Conclusions: AMP and PEN combined with gentamicin have similar effectiveness in the empiric treatment of suspected neonatal EOS.**	**16.Comparison of ampicillin plus gentamicin vs. penicillin plus gentamicin in empiric treatment of neonates at risk of early onset sepsis** Metsvaht T, Ilmoja M-L, Parm Ü, Maipuu L, Merila M, Lutsar I. Acta Pædiatrica **2010,** 99, pp. 665–672

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Search	Add to builder	Query	Items found	Time
		"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]))))) Filters: **Guideline; Meta-Analysis; Practice Guideline; Randomized Controlled Trial; Systematic Reviews; published in the last 10 years**		
#52	Add	Search **(((((((ampicillin) OR gentamycin) OR gentamicin) OR penicillin) OR "Ampicillin"[Mesh]) OR "Gentamicins"[Mesh]) OR "Penicillins"[Mesh])) AND ((((((((((((((("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])))))**	692	07:10:38
#51	Add	Search **((((((ampicillin) OR gentamycin) OR gentamicin) OR penicillin) OR "Ampicillin"[Mesh]) OR "Gentamicins"[Mesh]) OR "Penicillins"[Mesh]**	126300	07:10:12
#50	Add	Search **ampicillin**	36719	07:09:03
#49	Add	Search **gentamycin**	18655	07:08:45
#48	Add	Search **gentamicin**	27406	07:08:35
#47	Add	Search **penicillin**	96417	07:08:12
#46	Add	Search **"Ampicillin"[Mesh]**	24120	07:07:16
#43	Add	Search **"Gentamicins"[Mesh]**	17419	07:06:38
#40	Add	Search **"Penicillins"[Mesh]**	71071	07:05:17
#1	Add	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**	84329	06:16:37

ecent queries

Search	Add to builder	Query	Items found	Time
		neonate") OR "preterm neonates")) OR (("Infant, Premature"[Mesh]) OR "Infant, Low Birth Weight"[Mesh]))))		

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Search	Add to builder	Query	Items found	Time
#71	Add	Search **(((Chorioamnionitis) OR "Chorioamnionitis"[Mesh])) AND ((((((((((((((("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])))))** Filters: **Guideline; Meta-Analysis; Practice Guideline; Randomized Controlled Trial; Systematic Reviews; published in the last 10 years**	23	07:19:39
#64	Add	Search **(((Chorioamnionitis) OR "Chorioamnionitis"[Mesh])) AND ((((((((((((((("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])))))**	916	07:18:39
#63	Add	Search **(Chorioamnionitis) OR "Chorioamnionitis"[Mesh]**	3844	07:18:06
#62	Add	Search **Chorioamnionitis**	3844	07:17:43
#61	Add	Search **"Chorioamnionitis"[Mesh]**	2332	07:17:14
#1	Add	Search **((((((((((((((("premature infant") OR "premature infants") OR "premature newborn")**	84329	06:16:37

ecent queries

Search	Add to builder	Query	Items found	Time
		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]))))		