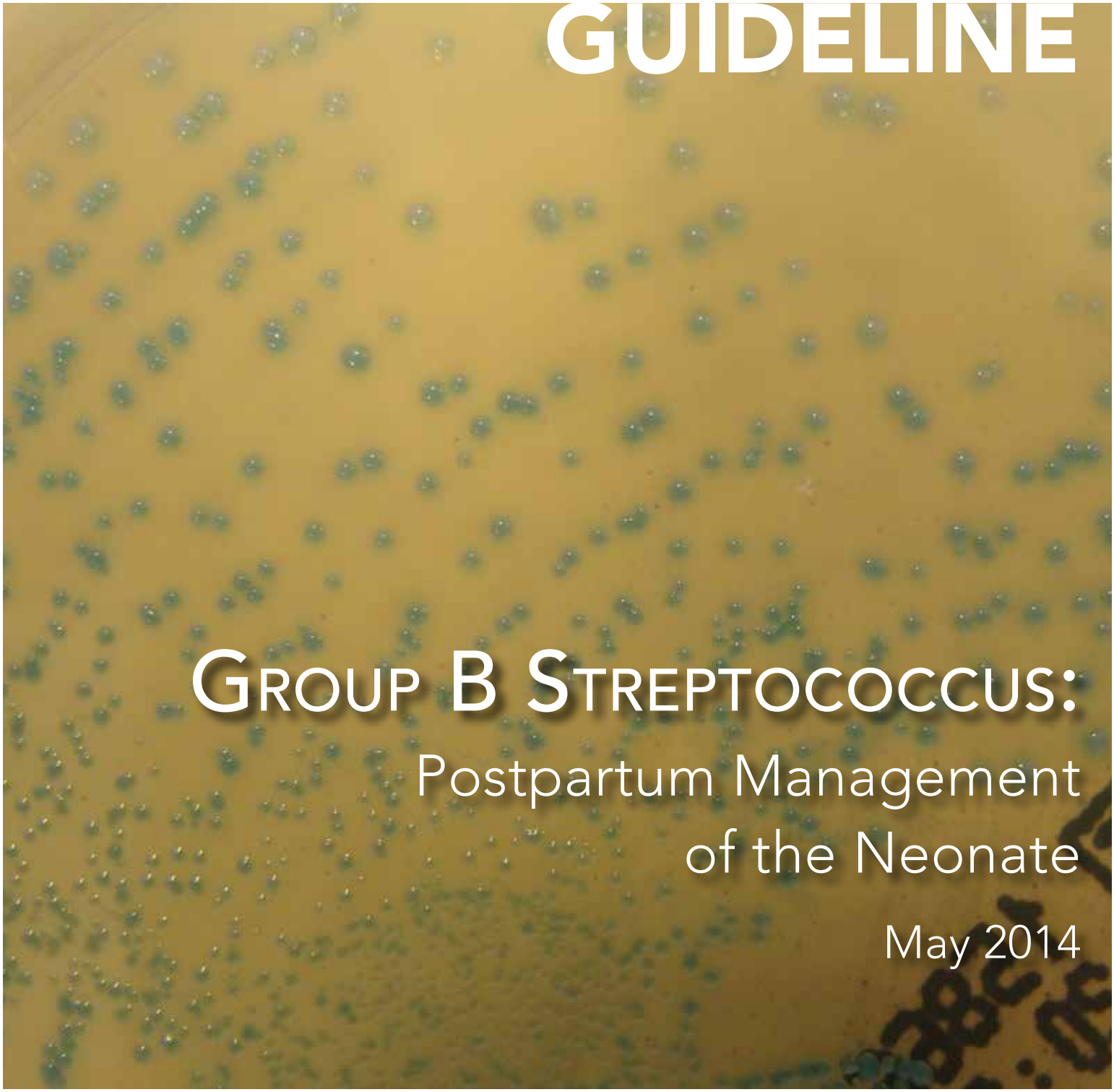
CLINICAL PRACTICE GUIDELINE 16



Group B Streptococcus:
Postpartum Management of the Neonate

May 2014

Association of Ontario Midwives
Delivering what matters.

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ACKNOWLEDGEMENTS

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This document may be cited as: PP GBS CPG Working Group. Association of Ontario Midwives. Postpartum Management of the Neonate. Available online.

Cover image:
Streptococcus agalactiae (Group B Streptococcus) on ChromID CPS chromogenic agar. Isolate obtained from a urine sample from a 32 year old full term (39 weeks) asymptomatic pregnant female. By Nathan Reading from Halesowen, UK [CC-BY-2.0 (http://creativecommons.org/licenses/by/2.0)], via Wikimedia Commons

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The AOM is committed, through our statement on Gender Inclusivity and Human Rights, to reflect and include trans, genderqueer and intersex communities in all aspects of our work.In this document, there are references to sources that use gendered language to refer to populations of pregnant and birthing people. In order to accurately represent these sources, we may have maintained gendered language. We support research and knowledge translation that engages and reflects the entire childbearing population.

2014: Approved by AOM Board of Directors.

2015: Minor edits were made to this guideline. For more information please contact the Association of Ontario Midwives.

Group B Streptococcus:
Postpartum Management of the Neonate

INTRODUCTION

Statement of purpose

The goal of this document is to provide an evidence-based clinical practice guideline (CPG) that is consistent with the midwifery philosophy and model of care. Midwives are encouraged to use this CPG as a tool in clinical decision-making. This CPG is independent of and not intended to replace the standards of the College of Midwives of Ontario (CMO).

Objectives

The objective of this CPG is to provide a critical review of the research literature on the management of Group B Streptococcus (GBS) during the neonatal period. This CPG is meant to complement and to be used in conjunction with AOM Clinical Practice Guideline No. 11 – *Group B Streptococcus: Prevention and Management in Labour* (2010). Evidence relating to the following will be discussed:

- Early-onset Group B streptococcal disease (EOGBSD) occurring in the first 7 days of life.
- Intrapartum risk factors for EOGBSD and management decisions for the newborn.
- Effectiveness and duration of intrapartum antibiotic prophylaxis (IAP).
- Neonatal management: assessment and monitoring for EOGBSD.

Outcomes of interest

Critical:

- Neonatal mortality
- Early onset GBS disease (sepsis/bacteremia, pneumonia, meningitis)
- Long-term sequelae of EOGBSD

Important:

- Potential harms associated with assessment/monitoring (pain/injury, separation of neonate and parent)

Abbreviations

CBC	complete blood count
CDC	Centers for Disease Control
CPS	Canadian Paediatric Society
EOGBSD	early onset Group B streptococcal disease
EOS	early onset sepsis
GA	gestational age
GBS	Group B streptococcus
GRADE	Grading of recommendations, assessment, development and evaluation
IAP	intrapartum antibiotic prophylaxis
NICU	neonatal intensive care unit
NNT	number needed to treat
OR	odds ratio
PROM	prelabour rupture of membranes
ROM	rupture of membranes
RR	relative risk
SOGC	Society of Obstetricians and Gynaecologists of Canada
WBC	white blood count

Methods

This CPG uses the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology for guideline development. Recommendations in this CPG are graded as either strong or weak according to the GRADE system. The strength of recommendation reflects the extent to which the Postpartum GBS CPG Work Group is confident that the benefits of a recommended intervention outweigh its harms, or vice versa. The strength of recommendation is influenced by the quality of supporting evidence, the balance between desirable and undesirable effects, and the perceived variability or uncertainty in clients' values and preferences with respect to the intervention.

The Work Group's judgements about the quality of evidence reflect the Work Group's confidence that available evidence correctly reflects the true effect of the intervention and is sufficient to support decision-making. Complete GRADE evidence tables used to summarize research and inform the recommendations are available in this guideline.

Appendix 1 provides further guidance to midwives and clients on the interpretation of GRADE recommendations. A full description of the AOM's policy and procedure for guideline development using GRADE is available on the AOM website.

STRENGTH OF RECOMMENDATION	The extent to which the CPG Work Group is confident that benefits of the recommended intervention outweigh its harms (or vice versa)
Strong	Benefits clearly outweigh risks and burdens (or vice versa). *Can be interpreted as:* • Most clients should be offered the intervention, assuming that they have been informed about and understand its benefits, harms and burdens. • Most clients would want the recommended course of action and only a small proportion would not.
Weak	Benefits, risks and burdens are closely balanced. *Can be interpreted as:* • The majority of clients would want the suggested course of action, but an appreciable proportion would not. • Values and preferences vary widely.

Based on: (1-4)

QUALITY OF EVIDENCE	How certain we ought to be about an estimate of effect or association
High	Further research is very unlikely to change confidence in the estimate of effect. • This evidence provides a very good basis for decision-making.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate. • This evidence provides a good basis for decision-making.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. • This evidence provides some basis for decision-making.
Very low	Any estimate of effect is very uncertain. • This evidence does not provide much of a basis for decision making.

Based on: (3-5)

Literature search

A search of the Medline and CINAHL databases and Cochrane library from 1995-2012 was conducted using the key words: group B streptococcus, pregnancy, early onset neonatal sepsis, assessment and monitoring. Additional search terms were used to provide more detail on individual topics as they related to postpartum GBS. Older studies were accessed in cases of commonly cited statistics, or significant impact on clinical practice.

Review

This CPG was reviewed using a modified version of the AGREE instrument, (6) the AOM Values-based Approach to CPG Development, (7) as well as consensus of the Postpartum GBS Working Group, CPG Committee, Insurance and Risk Management Program and the Board of Directors.

BACKGROUND

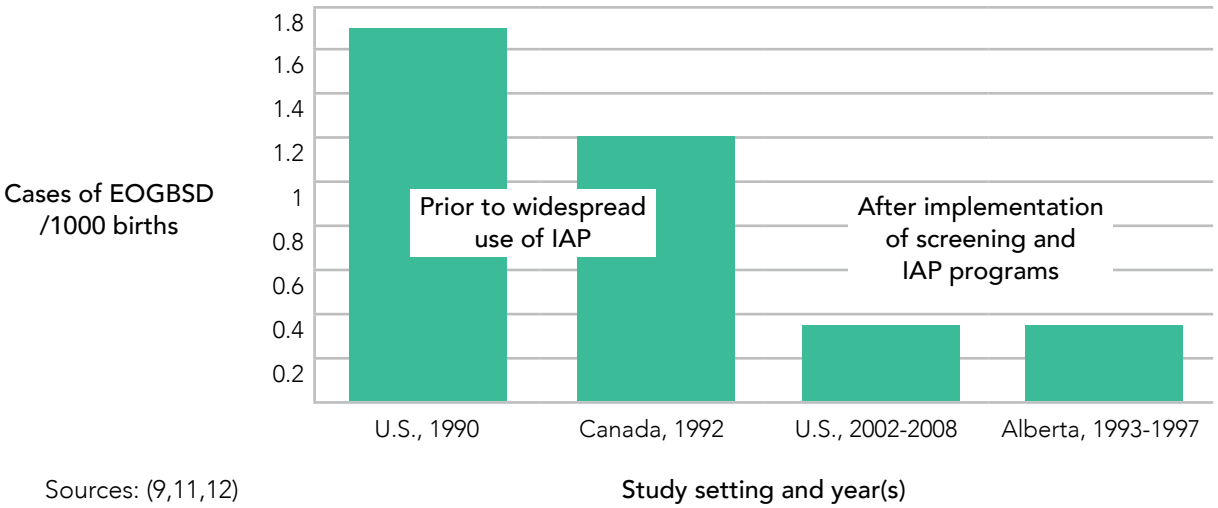
Incidence

The incidence of EOGBSD in Canada and the United States (U.S.) has declined significantly since the introduction of screening for colonization of GBS and implementation of IAP. (8) The observed incidence of EOGBSD in the setting of widespread screening and prevention strategies ranges from 0.3 to 0.89/1000 live births varying by individual study and site. In Canada, the rate is approximately 0.36/1000 live births. (9) Researchers at two Toronto tertiary care centres noted an incidence of EOGBSD of 0.92/1000 live births from 1995-2002. (10) According to the Centers for Disease Control and Prevention (CDC) the overall U.S. incidence is 0.34 to 0.37/1000 live births with 70% of cases occurring at term. (8,11) (See Figure 1.)

The epidemiology of EOGBSD in the context of universal screening

Current patterns of incidence of EOGBSD are paradoxical at first glance. While vaginal colonization with GBS is a necessary cause of EOGBSD, recent studies have established that 52% to 82% of term neonates who develop EOGBSD are born to individuals who screened negative for GBS prenatally. (13-16) It is unclear whether these cases are associated with a false-negative screening result or colonization after screening has occurred. The absolute risk of EOGBSD in the context of a negative prenatal screen is low. In the absence of IAP, EOGBSD is substantially more likely to occur in neonates born to individuals who test positive for GBS at prenatal screening; research conducted in the U.S. in the 1980s suggested that GBS colonization was associated with a greater than 25-fold increase in risk of giving birth to an infant with EOGBSD. (8,17) The provision of IAP to parturients who screen positive for GBS has been accompanied by a reduction in the incidence of EOGBSD in neonates born to that cohort, resulting in a relative increase in the proportion of EOGBSD cases associated with a negative prenatal screen (see Figure 1). (18,19)

FIGURE 1: OVERALL INCIDENCE OF EOGBSD



Sources: (9,11,12)

Intrapartum antibiotic prophylaxis

There are 3 approaches to identifying clients to whom to offer IAP: the risk factor strategy, the universal screening strategy and the screening with risk factors strategy. These approaches are described in Appendix 2 and explored in greater detail in AOM Clinical Practice Guideline No. 11 – *Group B Streptococcus: Prevention and Management in Labour.*(20) A Cochrane review assessing the effects of IAP provided to GBS-positive individuals, compared to no treatment, included 3 studies (852 participants). The review found no statistically significant differences in risk of neonatal mortality. While use of IAP was associated with a reduction in both confirmed EOGBSD (relative risk (RR) 0.17, 95% CI 0.04-0.74) and probable EOGBSD (RR 0.17, 95% CI 0.03-0.91), the high risk of bias in the included studies led the authors to conclude that IAP provided on the basis of a positive GBS screen is "not supported by conclusive evidence from well designed and conducted randomized controlled trials." (21)

Which risk factors are most likely to be associated with EOGBSD?

Antenatal and intrapartum risk factors for EOGBSD are explored in greater detail in AOM Clinical Practice Guideline No. 11 – *Group B Streptococcus: Prevention and Management in Labour.* (20)

Considering maternal risk factors that arise during the antenatal and intrapartum period is an essential component in decision making for the management of the neonate in the early postpartum period. A summary of maternal risk factors associated with EOGBSD in the neonate is provided here for ease of reference. Research studies examining risk of EOGBSD in the presence of different risk factors vary in quality. Available research in many cases was conducted prior to widespread GBS screening and implementation of prevention strategies or is difficult to compare as different studies used varying prevention strategies limiting external validity.

Maternal GBS colonization is the primary risk factor for EOGBSD. Researchers have also identified a handful of intrapartum factors associated with an increased risk of EOGBSD:

- **Gestational age and birth weight**. Preterm and/or low birth weight infants are at significantly higher risk of EOGBSD than term infants. (10,14)
- **Intrapartum fever**. Intrapartum fever (temperature ≥38.0°C) is a non-specific indicator of maternal and/or neonatal infection. A key criterion for the diagnosis of clinical chorioamnionitis, maternal intrapartum fever may also result from increased metabolic activity or poor ventilation, or as a consequence of epidural analgesia. (22-25)
- **Chorioamnionitis**. Researchers have noted a relatively high frequency of maternal fever and chorioamnionitis in neonates who developed EOGBSD despite the administration of IAP, suggesting that chorioamnionitis may be a marker of high risk for EOGBSD. (17,26-28) The Canadian Paediatric Society (CPS) notes that the risk of sepsis (due to all causes) for the infant whose parent has "definite" chorioamnionitis (fever, left-shift WBC and lower uterine tenderness) is 8%, while the risk is 3% to 4% when "definite" and "probable" chorioamnionitis is combined. (29)
- **Duration of rupture of membranes**. In a case-control study in which IAP use was widespread, and overall risk of early onset sepsis (EOS) was consequently low, Puopolo and colleagues observed a nearly linear relationship between length of rupture of membranes and risk of EOS (all causes), with risk increasing with duration of prelabour rupture of membranes (PROM). (30) Studies show risk of EOGBSD increasing with PROM of varying length, but generally risk increases significantly across studies with PROM ≥ 18 hours. (17,31)
- **Specific obstetrical practices**. Practices such as frequency of intrapartum vaginal examinations and intrauterine fetal monitoring have been variably associated with increased risk of EOGBSD in observational studies. (31,32) Because such practices may be used more frequently in the presence of other risk factors, this relationship may be confounded. (8)

Because much of the research pertaining to risk factors was conducted prior to the widespread implementation of GBS screening, little is known about how these risk factors relate to or are affected by GBS status or how they are modified or attenuated by use of IAP. Odds ratios (ORs) for risk factors associated with EOGBSD from one review based on findings of studies published from the 1960s to the mid-1990s (17) are listed in Table 1.

TABLE 1: ANTENATAL AND PERINATAL RISK FACTORS ASSOCIATED WITH EOGBSD: BENITZ REVIEW (PEDIATRICS, 1999)

Risk Factor		Association with EOGBSD Estimated (pooled) OR
GBS status known	Maternal vaginal GBS culture at delivery	204
	Maternal rectovaginal GBS culture at 36 weeks' GA	26.7
GBS status not known	Low birth weight (≤ 2500g)	7.33
	PROM > 18 hours	7.28
	Chorioamnionitis	6.43
	Intrapartum fever (> 37.5˚C)	4.05
	Preterm birth (<37 weeks)	4.83

Notes:

- Study data was collected prior to GBS screening and use of IAP.
- Fever is variably defined, but is typically considered to be clinically relevant when intrapartum temperature ≥38.0˚C (100.4°F). Researchers have observed risk of sepsis increasing with intrapartum temperature: In a case-control study in which IAP use was widespread, intrapartum temperature above 39.2˚C (102.5˚F) was associated with 4 times the risk of EOS than a fever between 38.1 - 38.6˚C (100.5 - 101.4˚F). (30)

Research suggests that intrapartum risk factors are absent in 30-50% of EOGBSD cases. (10,16,33) Intrapartum risk factors were absent in 41% of cases of EOGBSD included in one observational study of EOGBSD at an American hospital from 1995-1999 (N=32). In cases in which risk factors were present, maternal fever or presumed chorioamnionitis were the most frequently identified, present in 79% of neonatal cases associated with maternal risk factors. (27)

GBS negative clients with risk factors

Although rare, neonates born to individuals who are GBS negative may also develop EOGBSD. The majority of cases of EOGBSD diagnosed in the current context occur in infants born to pregnant people who screened negative at 35 to 37 weeks gestation and who did not receive IAP. Though infants born to clients who screen negative for GBS at 35 to 37 weeks gestation are at low risk of developing EOGBSD an overview of risk factors that increase risk of neonatal infection in general is provided. In one U.S. study, intrapartum risk factors were absent in 43% of cases of EOGBSD that occurred in term infants whose parents had screened GBS negative during pregnancy. (16)

Chorioamnionitis and/or maternal fever

Based on data from one large U.S. based study conducted after GBS screening and IAP became routine, (14) researchers estimated a 0.334% risk of EOGBSD among term infants born to GBS negative women diagnosed with chorioamnionitis. (34) A large retrospective cohort study found that the absolute risk of early neonatal death related to an infection (caused by any organism) was 1/10 000 births in which intrapartum fever was present. The authors of this study were unable to consider the possible contributions of epidural anesthesia. (22)

Prelabour rupture of membranes (PROM)

A Cochrane review comparing induction of labour and expectant management for individuals with PROM at term showed no difference in rates of neonatal infection. (35) A 1% neonatal infection rate for PROM > 24 hours is generally accepted in the research literature. (36) though the neonatal infection rate in the Term PROM trial was 2% (induction arm) and 2.8% (expectant arm). (37) Refer to AOM Clinical Practice Guideline No. 13 – *Management of Prelabour Rupture of Membranes at Term* (2010) for guidance on management strategies for clients with PROM at term. (38)

Modeling to predict risk

A multivariate predictive model that predicts individualized risk of early onset sepsis has been developed (all causes) based on objectively-assessed

intrapartum factors (gestational age, highest intrapartum temperature, length of ROM, GBS status, and type and duration of IAP). (30,39) This model is based on data from a case-control study conducted in California and Massachusetts. (30) Cases had culture-proven EOS at < 72 hours and were ≥ 34 weeks' gestational age; GBS was identified as the causative organism in 53.1% of cases, corresponding to an overall incidence of EOGBSD of approximately 0.31/1000 births. (30) GBS IAP was provided at each of the 14 hospital sites involved in the study, using either a risk factor-only or screening-based approach. After controlling for confounders, the following factors were associated with increased risk of developing EOS: positive GBS status, gestation of < 37 and ≥ 41 weeks, intrapartum fever, and ROM > 12 hours. The provision of any antibiotic ≥ 4 hours before birth was associated with a decreased risk of infection. (30)

An advantage of this model is that it is able to conceptualize cumulative risk in the presence of multiple risk factors and modify risk in the presence or absence of IAP. A drawback of the model is that it estimates risk of sepsis generally, rather than EOGBSD specifically. While cases were derived from a large birth cohort (608 014 live births), the number of affected cases is ultimately small (n=350) and the researchers were unable to generate stable predictive models for all possible combinations of GBS status and IAP agent. (30)

This model predicts "prior probability": an estimate of risk based on observed rates of sepsis in the case-control study upon which the model is based, to then combine with subsequently-available information (e.g. laboratory or clinical examination findings) to guide evaluation and treatment decisions. Because it is derived from data collected in U.S. hospitals in which GBS screening strategies were in place and IAP was widely used, midwives may find this model helpful in estimating a neonate's risk of EOS, relative to an overall neonatal population, to incorporate into discussion with parents and decision-making around evaluation and treatment. (30,39) The model has not, however, been thoroughly tested or validated.

An online risk calculator based on this model may be found at:

http://www.dor.kaiser.org/external/DORExternal/research/infectionprobabilitycalculator.aspx.

SUMMARY POINTS

- Most EOGBSD cases now occur in neonates born to parents who have screened negative for GBS by rectovaginal culture at 35 to 37 weeks' gestational age. This trend reflects the limitations of current methods of assessing colonization status, as well as the relative decrease in incidence of EOGBSD among individuals targeted for IAP based on a positive prenatal screen.

RESEARCH GAPS

- Accurate methods of intrapartum GBS testing are needed to ensure that GBS status at birth is correctly identified and IAP is offered appropriately. To provide equity in access and care such a test should ideally be available in a variety of settings, including hospital, home and in birth centres.
- Researchers have yet to identify maternal and intrapartum characteristics that identify at-risk neonates with accuracy and precision. Studies that assess infection-related outcomes in large cohorts of infants, stratified based on maternal GBS colonization and intrapartum antibiotic treatment and treatment strategy, are needed.

PREVENTION OF EOGBSD IN THE NEONATE

The following focuses on the issue of prevention and management of EOGBSD after birth. For a discussion and recommendations on antenatal screening for GBS and indications for IAP please refer to AOM Clinical Practice Guideline No. 11 - *Group B Streptococcus: Prevention and Management in Labour.* (20)

Are there effective strategies for preventing EOGBSD in the well-appearing newborn?

A literature search did not identify any effective strategies to prevent EOGBSD during the postpartum period beyond vigilance in identifying clinical signs of sepsis.

Neonatal bathing

No evidence was found evaluating the practice of bathing newborns after birth to prevent neonatal infection and sepsis. One study was found comparing soap to plain water for the first bath. This study found no difference between the two methods in type or quantity of bacteria colonized in the newborn. (40) There were no studies identified comparing no bath to any bathing.

Does chlorhexidine skin cleansing prevent EOGBSD?

There is a small body of literature on cleansing newborns' skin with chlorhexidine to prevent neonatal sepsis and subsequent morbidity or mortality. All randomized trials identified since 2000 have been completed in low-resource settings where baseline risks of neonatal sepsis and mortality are much higher than in Canada. There is conflicting evidence as to whether chlorhexidine bathing reduces bacterial transmission and improves neonatal outcomes in areas of high baseline risk. (41-43) Two studies from Nepal showed a very weak benefit of neonatal skin-cleansing to very low birth weight newborns (<2500g). (44) A study from Pakistan did not show any effect on perinatal mortality or neonatal sepsis. (45) Differences in pathogen prevalence patterns limit the applicability of these findings to the Canadian context: gram-negative pathogens are responsible for most neonatal sepsis mortality in low-resource settings. (46)

See the GRADE evidence profile tables for an evidence quality summary. GRADE evidence profiles were limited to studies that included GBS status on entry (From (41)).

Adverse effects of chlorhexidine

Percutaneous absorption occurs at trace levels following topical applications of chlorhexidine, particularly in preterm newborns. Reported concentrations appear to be safe, but a maximum dose of chlorhexidine has not been identified. There are no reports of adverse health consequences as a result of absorption of chlorhexidine in newborns. Tens of thousands of neonates have received a range of chlorhexidine-based cleansing interventions without reported adverse effects, including birth after lavage of the vagina, full-body cleansing, and umbilical cord cleansing. Transient contact dermatitis has been reported in preterm very-low-birth-weight infants after long-term (> 7 days) exposure. (47)

A growing body of research has explored the development of the infant microbiome and its subsequent impact on longer-term health outcomes. (48,49) While most of this research focuses on the microbiota of the neonatal gut, other microbial habitats (such as on the skin) also appear to be influenced by birth-related factors. Initial research suggests that vaginal microbiota may provide vaginally-born infants with an important first exposure to microbes that serve an important defensive role, occupying pathogenic niches as the neonatal skin microbiome matures and site-specific bacterial communities develop. (50) Rapid surface colonization coincides with significant changes in the barrier function of the skin as the neonate transitions from the aqueous, sterile environment of the uterus to a gaseous environment with constant microbial interaction. This process continues throughout the first months and years of life. (51,52) While available research suggests that chlorhexidine washing is not associated with immediate ill effects, the implications of chlorhexidine use have not been explored in light of researchers' evolving understanding of the neonatal skin microbiome. It is possible that chlorhexidine bathing may interrupt early microbial colonization of the skin of the neonate, affecting the development of the skin's immune function, and potentially the development of the systemic immune system.

SUMMARY POINTS

- High and moderate-quality studies conducted in low-resource countries provide conflicting evidence that chlorhexidine bathing of the newborn reduces bacterial transmission and/or colonization of the neonate. It is unknown whether this results in a significant reduction in EOGBSD morbidity or mortality. There is no evidence of harm in its use.
- The applicability of these findings to the Canadian context is limited by differences in setting and patterns of pathogen prevalence. Midwives may choose to share information about chlorhexidine with clients who feel strongly about avoiding use of systemic antibiotics and are interested in considering other interventions to limit risk of EOGBSD.
- While available research suggests that chlorhexidine washing is not associated with immediate ill effects, the implications of chlorhexidine use have not been explored in light of researchers' evolving understanding of the neonatal skin microbiome. Midwives should inform clients of the theoretical longer-term impacts of chlorhexidine use when discussing its use.

RESEARCH GAPS

- There is no evidence on the effects of bathing neonates versus no bathing on risk of neonatal sepsis.
- Further research is needed to establish the potential benefits of chlorhexidine bathing of the neonate, as well as any risks such interventions pose in terms of early microbial colonization of the infant's skin.

INTRAPARTUM ANTIBIOTIC PROPHYLAXIS: POSTPARTUM CONSIDERATIONS

The section below addresses IAP-related considerations after birth. For a discussion of antenatal and intrapartum considerations related to IAP please refer to AOM Clinical Practice Guideline No. 11 - *Group B Streptococcus: Prevention and Management in Labour.* (20)

IAP and the clinical course of EOGBSD

Several studies have found no significant differences in the timing or symptoms of clinical onset of EOGBSD between infants exposed to IAP and those who were not. (8,13)

IAP causing negative blood cultures

There is a limited amount of evidence examining the effect of IAP on the sensitivity of blood cultures. In a case-control study involving neonates who were subsequently diagnosed with EOS (all causes), prenatal antibiotic therapy was associated with an increased likelihood of a negative cord blood culture at birth. (53) Other studies suggest a reduced sensitivity of blood cultures when the neonate has been exposed to IAP. (8)

Assessment of adequacy of IAP

CPS and CDC guidelines define adequate IAP as ≥ 4 hours of IV penicillin, ampicillin or cefazolin before birth.(8,29) Recommended antibiotic regimens are described further in AOM Clinical Practice Guideline No. 11 – *Group B Streptococcus: Prevention and Management in Labour.* (20)

Researchers have attempted to establish whether neonatal management strategies ought to be modified based on type and duration of intrapartum antibiotic. One question is how to manage neonates born to GBS positive clients who have received 'inadequate' IAP (variously defined as IAP < 4 hours prior to birth or no IAP, or IAP with clindamycin, erythromycin or vancomycin).

While not specified in the CDC's management algorithm, the IAP regimens recommended by the CDC and Society of Obstetricians and Gynaecologists of Canada (SOGC) specify additional doses of antibiotic every 4 (penicillin, ampicillin) to 8 (cefazolin, clindamycin) hours after the initial dose. (8,54) The initial rationale behind the choice of 4 hours as the definition of adequate IAP is unclear. It is difficult to

assess the adequacy of IAP with durations of < 4 hours for the prevention of a rare outcome such as EOGBSD because of the large number of study participants required. Studies have therefore used surrogate outcomes such as neonatal GBS colonization and concentration of antibiotics measured in maternal serum, fetal serum, and amniotic fluid. Several studies suggest that penicillin G and ampicillin reach bactericidal levels in fetal serum or amniotic fluid sooner than 4 hours, and then begin to decline, reaching a nadir approximately 4 hours after administration. (55-58)

A prospective study examined the relationship between duration of IAP and fetal serum penicillin G levels among 98 term infants of GBS-positive parturients.(56) Antibiotic levels in cord blood samples were 10-179 times higher than the minimal inhibitory concentration (the lowest concentration of an antimicrobial that will inhibit the visible growth of a microorganism after overnight incubation). The highest inhibitory concentrations were seen approximately 1 hour after the loading dose (5 million units). In participants receiving subsequent doses every 4 hours, levels remained consistently above minimal inhibitory concentration. (56) The results suggest that durations of IAP shorter than 4 hours are effective in attaining bactericidal levels of antibiotics for GBS, and that fetal serum levels do not build with time, but decline at four hour intervals. Adherence to dosing every 4 hours, independent of duration of IAP, should be a priority.(56)

A second study measured GBS colonization in neonates receiving no IAP or < 4 hours of ampicillin. The study included only GBS-positive participants (GBS status confirmed within 48 hours of birth) without other risk factors and healthy neonates ≥ 37 weeks' GA. Neonatal colonization with GBS was significantly reduced with partial IAP (1 dose < 4 hours prior to birth) compared to no IAP ($p < .001$). These findings suggest that partial IAP can reduce risk of GBS transmission in individuals without other risk factors for EOGBSD and support the administration of IAP for clients choosing it regardless of length of labour. (57)

A secondary analysis of data from a U.S. infectious disease surveillance program is the first published study that directly assessed the effectiveness of IAP on EOGBSD-related outcomes in a context in which GBS screening is widespread. The authors compared incidence of culture-proven EOGBSD among cases and matched controls identified in a population of more than 600 000 liveborn infants. Comparing risk for EOGBSD among neonates born to parents receiving IAP and those receiving no prophylaxis, the study's authors found that IAP with penicillin or ampicillin for duration of ≥4 hours was associated with a 89% reduction in risk of EOGBSD ($p < .001$). Shorter durations of IAP were associated with reduced levels of effectiveness: IAP with penicillin or ampicillin for durations of <2 and 2-4 hours resulted in 47% and 38% reductions in risk, respectively; these estimates of effect were not statistically significant. Despite the large size of the original surveillance population, the study had insufficient power to detect statistically-significant differences in EOGBSD among neonates born to the subset of participants who received shortened durations of IAP. Further research is needed to increase confidence in the effects noted. (59)

SUMMARY POINTS

- IAP may be considered 'adequate' if a client has received intravenous penicillin, ampicillin or cefazolin for ≥ 4 hours before delivery.
- Clindamycin, erythromycin and vancomycin are always considered 'inadequate' for the purpose of neonatal management because neither efficacy nor effectiveness has been conclusively demonstrated.
- Because bactericidal levels do not build with time, but decline at four hour intervals, adherence to dosing every 4 hours, independent of duration of IAP, should be a priority.
- Several studies have demonstrated that IAP reaches bactericidal concentrations in amniotic fluid and/or fetal serum in < 4 hours. (55-58) One study suggests that durations of IAP less than 4 hours are less effective at preventing EOGBSD than a full course of treatment. Further studies are required to replicate and increase confidence in these findings. (59)

RESEARCH GAPS

- More research is needed on the efficacy of alternative IAP regimens to reduce the incidence of EOGBSD in the newborns of penicillin-allergic individuals.

EOGBSD AND THE ASSESSMENT AND MONITORING OF THE NEONATE

Identifying EOGBSD in the neonate

Management recommendations from both the CPS's guideline on *Management of the Infant at Increased Risk for Sepsis* (29) and the CDC's guideline on the *Prevention of Perinatal Group B Streptococcal Disease* (8) are referred to in discussions related to midwives' postpartum management of the neonate. Recommendations for care of infants born to clients who are GBS positive relate to aspects of care that are in the midwifery scope of practice. Midwifery management of the neonate in the early postpartum period typically involves: monitoring and assessment of the well newborn; identifying and providing parental education about signs of EOGBSD (sepsis) and consulting as required according to CMO's Consultation and Transfer of Care Standard. (60) It is suggested that midwives discuss recommendations in the CPS and CDC algorithms for postpartum management of the infant, as well as the recommendations in this guideline and any applicable hospital protocols as part of informed choice discussions for management decisions. In addition, midwives should inform parents of likely care plans once a consultation is initiated.

EOGBSD is a low incidence but potentially disabling or fatal condition. None of the GBS prevention strategies currently available will prevent all cases of EOGBSD. As current incidence patterns demonstrate, EOGBSD can occur in the presence of a negative prenatal screen; EOGBSD may similarly occur despite the administration of IAP. As primary care providers, midwives must be skilled in assessing and monitoring for sepsis in the neonate and recommending use of diagnostic tests appropriately.

Researchers have identified numerous signs associated with neonatal sepsis. The majority of these signs are non-specific, subjectively assessed, and relatively weak predictors of EOGBSD. Most research on the clinical manifestations of sepsis address severe bacterial illness generally, rather than EOGBSD specifically. (61) EOS (all causes) was diagnosed in only 3.2% of all symptomatic infants evaluated for sepsis in one study of neonates ≥37 weeks' GA. (62)

TABLE 2: SIGNS ASSOCIATED WITH EOGBSD

- Apnea (unexplained episode of cessation of breathing for 20 seconds or longer) (63)
- Lethargy / irritability
- Poor feeding
- Poor peripheral perfusion
- Respiratory distress
- Tachycardia
- Temperature instability (fever is very uncommon)
- Hypoglycemia (uncommon)
- Uncommon physical findings: skin lesions, petechiae, organomegaly

Source: (29,64)

Decision-making is straightforward in the presence of unequivocal signs of illness. The CPS emphasizes that the progression of EOGBSD is very rapid, and therefore any neonate with clinical signs suggestive of infection (Table 2) should receive immediate assessment and consultation for treatment. Delay between recognition of signs of sepsis and initiating therapy increases the risk of a poor outcome. (29)

The well-appearing neonate

In the absence of signs of illness, decision-making around the assessment of EOGBSD is less clear. EOGBSD may be initially asymptomatic, and signs of illness may be equivocal and/or transient in infants with and without EOGBSD. Research suggests that initial asymptomatic status is a strong negative predictor of culture-proven EOGBSD: infants who appear well will most likely remain well. (29,65,66) In one study of 1568 neonates who did not receive IAP, initial asymptomatic status was associated with a significantly decreased risk of infection (Adj. OR 0.26; 95%CI 0.11-0.63). (67) Efforts to create risk prediction models that consider infant clinical status are ongoing. (39)

The CPS and CDC guidelines on the prevention of EOGBSD include neonatal care pathways that take GBS status and infant well-being into account, as well as the presence or absence of a handful of intrapartum risk factors: presence of chorioamnionitis, gestational age, duration of ROM and whether full IAP was given. (8,29) Please refer to Appendix 3 for CPS and CDC care pathways. Researchers have long struggled to identify factors that increase risk of EOGBSD to a point that warrants preemptive evaluation of the neonate and/or treatment. Researchers estimate that the application of a standard neonatal care pathway will result in the evaluation of approximately 15% of all term and near-term infants. (30,65)

Expectant observation of the asymptomatic newborn is supported by a limited amount of observational data, including a cohort study involving 1413 pairs of partially-treated parents and infants. One case of culture-proven EOGBSD was noted, corresponding to an incidence equivalent to 0.7/1000, similar to the overall incidence noted in the study population. (68)

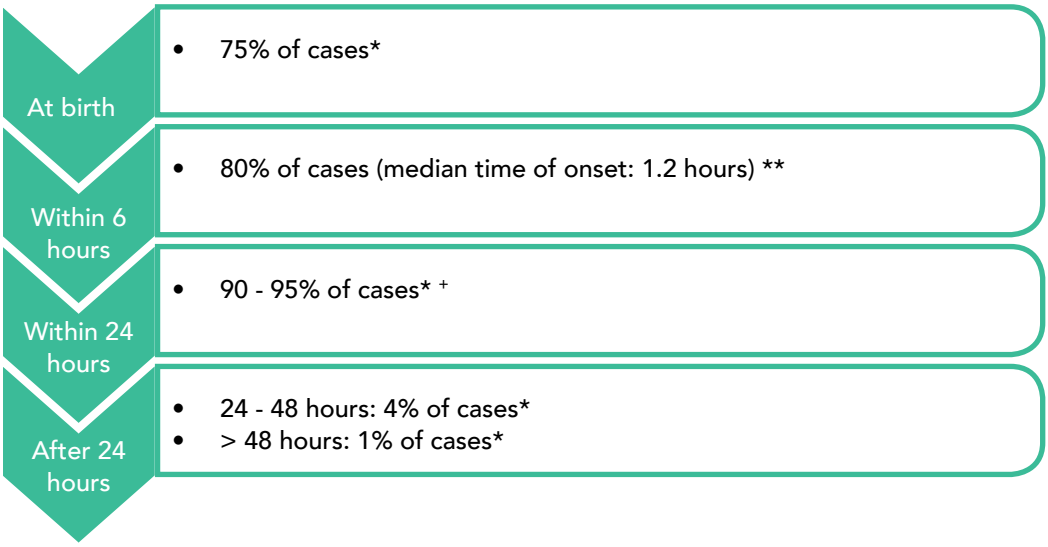
While the observed timing of onset of EOGBSD varies by study and method of assessment or diagnosis, studies consistently suggest that most cases of EOGBSD occur soon after birth. In one study, researchers found that 80% of EOGBSD cases with positive blood cultures, and 95% of clinically suspected cases, were symptomatic by 6 hours. Patterns of onset were similar in a subset of neonates exposed to IAP. (13) Proportions of EOGBSD cases with onset within 24 hours varied from a low of 60% to 70% in multi-centre trials to a high of 95% in a single study. (69,70) The CDC estimates that overall, 90% of EOGBSD cases present within 24 hours. (8)

Most of the remaining cases of EOGBSD occur within 24 to 48 hours of birth. The CPS estimates that 4% of EOGBSD cases present between 24 and 48 hours, while the remaining 1% of cases present after 48 hours. (29) A study of 127,205 neonates in the U.S. observed rates of 7% and 4% after 24 and 48 hours respectively. (15)

See Figure 2 for a summary of the research on timing of onset of clinical signs of EOGBSD.

Timing of onset of clinical signs of EOGBSD

FIGURE 2: TIMING OF ONSET OF CLINICAL SIGNS OF EOGBSD



Sources:
*(29)
** (13)
+ (8)

Clinical versus culture-proven sepsis

Clinical sepsis: Clinician-diagnosed sepsis lacking culture confirmation. Diagnosis is made based on clinical symptoms and elimination of other possible causes.

Culture-proven invasive sepsis: Pathogen has been isolated from a sterile site culture (blood, cerebrospinal fluid).

Recent trends in clinical (or unproven) sepsis have not been well-described, and they may differ from trends in culture-proven invasive sepsis. U.S. data suggests that an estimated 7% to 15% of all term and near-term neonates are evaluated for sepsis, due to clinical signs as well as existing risk factors. Only 3% to 8% of those evaluated will go on to have culture-proven sepsis. (65,71) In a cross-sectional study of all US hospital admissions for sepsis (all causes) from 1988-2006, the estimated incidence of clinical sepsis was 10 times higher than proven invasive sepsis. (72) In a Spanish study involving 107,021 births, rates of culture-proven versus clinical EOGBSD were 0.39 and 0.47/1000 respectively. (73)

In Canada from 2003-2008 the rate of culture-proven sepsis in 26 tertiary hospital neonatal intensive care units (NICUs) was 6-7/1000 NICU admissions (for any diagnosis). Of this, GBS accounted for 1.9/1000 admissions, representing 27% to 32% of cases of sepsis. It is unclear how many of these neonates had signs of sepsis at birth. (74)

What is appropriate assessment and monitoring?

In general, the value and accuracy of clinical assessment activities for EOGBSD are difficult to evaluate. There is no clear distinction between EOGBSD and other early-onset infections in the clinical signs that may present, and non-infectious neonatal disorders may share similar signs. (75) Conventional monitoring practices (e.g. assessment of vital signs or clinical signs at specified intervals) have not been evaluated for their impact on clinical outcomes.

Consequently, recommendations on monitoring for signs of sepsis are based on consensus, rather than research demonstrating efficacy. (75-77) While CPS and CDC guidelines recommend observation (or "close observation") of well-appearing infants at increased risk of EOGBSD, these guidelines are silent as to what such observation should entail. (8,29)

A midwifery evaluation of the newborn to identify signs of sepsis in the newborn will typically include:

- Taking a history from parents about signs of sepsis noted, including: newborn behaviour, feeding and their observations about breathing and colour.
- Taking the newborn's vital signs, including:
  - » monitoring the newborn's breathing rate as well as evaluating for signs of respiratory distress (grunting, nasal flaring, retractions of intercostal muscles or sternum, see-saw respirations)
  - » heart rate, heart sounds
  - » temperature (hypothermia, temperature instability)
- Evaluation of the newborn's colour (evidence of pallor, mottling, cyanosis), muscle tone, state of consciousness (stupor, irritability), quality of movements and cry, presence of reflexes, feeding behaviour/patterns (poor feeding)
- Oxygen saturation (SpO_2), if monitoring is available

Setting of assessment

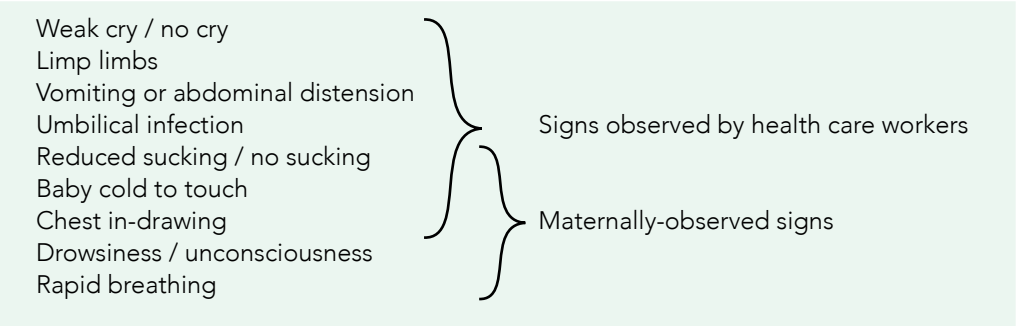
Midwives regularly monitor and assess newborns for signs of sepsis. As community based practitioners, midwives may conduct assessments and monitor the newborn in the home, clinic, birth centre or hospital. Midwives also respond to telephone inquiries from parents about their newborns, give advice by phone and determine the urgency and necessity of an in-person assessment of the newborn as needed. After discussing concerns with parents, midwives use clinical judgment and consider local community factors to determine whether clinical evaluation of the newborn should occur in the clinic, home, birth centre or hospital.

Home-based monitoring

While parents may be well-equipped to monitor for potential signs of sepsis in their newborn's first few days of life, there is little research available to guide midwives in preparing parents for such monitoring.

No research was found on the assessment and monitoring of the neonate specific to EOGBSD in the home setting. Similarly, no research was found from

TABLE 3: SIGNS OF SEPSIS OBSERVED IN THE HOME SETTING (INDIA) (78)



high resource settings evaluating the utility of midwives or other health professionals educating parents on monitoring for signs of sepsis. One randomized control trial on home-based care by minimally trained village health workers in India developed a list of the most sensitive signs of sepsis reported by village health workers and mothers (see Table 3). However, GBS was less prevalent than in Canada and many neonates were low birth weight. (78) In addition, all causes of sepsis, both early and late, were included and the setting and skill level of the provider are not comparable to midwifery care in Canada. In a secondary analysis, the mothers' observations of signs of sepsis in the neonate that were significantly associated with a diagnosis of sepsis by the health care worker were also collected. These are listed in Table 3.

Midwives may look to parents to play an active role in identifying potential signs of sepsis while caring for and interacting with their newborns, provided that:

- Parents are deemed to be capable of identifying concerning signs of sepsis (see Table 2);
- Parents will be able to contact the midwife and access urgent care if necessary.

Hospital–based monitoring

Both CPS and CDC guidelines recommend expectant observation of the well-appearing newborn who has received adequate IAP. Recommendations for length of observation for these neonates differ slightly. The neonatal care pathway included in the CDC's 2010 guidelines recommends ≥ 48 hour observation (in hospital) of well-appearing infants whose parents received adequate IAP in labour but suggests that discharge as early as 24 hours may be permitted "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." (8) CPS guidelines suggest that discharge at 24 hours is reasonable provided that parents are counselled on how to access health care resources in the event that signs of sepsis are noted. (29)

U.S.-based researchers recently published a simulated comparison of hospital-based observation strategies for term neonates born to GBS-positive parturients who received adequate IAP. (79) Aggregating data from existing published data, the researchers compared cost-effectiveness and clinical outcomes based on discharge of asymptomatic infants at 24 or 48 hours post-delivery. The researchers concluded that discharge at 24 hours is a more cost effective option; delaying discharge to 48 hours was associated with substantial additional costs and only minimal improvements in health outcomes (Table 4). (79)

For well-appearing infants at term whose parents are GBS positive and did not receive ≥ 4 hours IAP, CPS guidelines recommend a CBC and 24 hours of close observation. (29) The CPS estimates that prolonging hospitalization from 24 to 48 hours for asymptomatic infants born to GBS positive parents who did not receive IAP ≥ 4 hours represents a number needed to treat (NNT) of 2000. (29) CDC guidelines recommend only observation ≥ 48 hours as long as there are no additional risk factors. If PROM ≥ 18 hours is also present, the CDC recommends CBC and blood culture at birth and/or 6 to 12 hours of life and observation ≥ 48 hours. (8)

Timing of assessment

No relevant research was found on the optimal timing of assessment of signs of sepsis in the newborn. The first 24 hours of life is the most critical period of assessment for EOGBSD as approximately 90% to 95% of cases of EOGBSD will present during this time. (8,29)

TABLE 4: OUTCOMES OF DELAYED HOSPITAL DISCHARGE

Estimated probability of EOGBSD-related death Asymptomatic term neonates born to GBS+ individuals who received IAP ≥ 4 hours		
If observed in hospital for 24 hours post-birth	0.00066%	or 1 / 151 515
If observed in hospital for 48 hours post-birth	0.00043%	or 1 / 232 558
Estimated probability of long-term health sequelae* Asymptomatic term neonates born to GBS+ individuals who received IAP ≥ 4 hours		
If observed in hospital for 24 hours post-birth	0.00198%	or 1 / 50 505
If observed in hospital for 48 hours post-birth	0.00146%	or 1 / 68 493

*not defined or explained
Source: (79)

Effects of sepsis evaluation

It is acknowledged that neonatal sepsis is over-evaluated and over-treated. (80) The unique circumstances of EOGBSD may make some over-evaluation unavoidable: clinical signs are varied and non-specific, the disease is rare, and risk of mortality increases with delayed treatment. Furthermore, since tests for sepsis take a long time and are not particularly definitive, clinicians may suggest treatment while results are pending or regardless of their eventual outcome.

No research was found on the qualitative experience of neonatal sepsis evaluation. Clinical and laboratory investigations undertaken to rule-out sepsis may involve blood draws, chest X-ray, lumbar puncture, NICU admission, and separation of neonate from parent and family. Although difficult to quantify, these procedures may result in pain for the neonate. Parents may experience anxiety while waiting for results even though the absolute risk of actual infection and/or serious outcomes is rare. Neonates may be unnecessarily exposed to antibiotics for empiric therapy pending laboratory results.

How effective is a complete blood count and/or blood culture in detecting EOGBSD in the well-appearing newborn?

The complete blood count (CBC) is commonly used to aid in the diagnosis of neonatal sepsis when guidelines or clinical judgement suggests that further diagnostic evaluation is warranted. The CBC includes a white blood cell count (WBC), differentials and platelet count. (29)

> Canadian paediatricians define an abnormal WBC count in the newborn as a total WBC of 5.0 x109/L or lower, or 30x109/L or greater, or an absolute polymorphonuclear cell count of less than 1.5 x 109/L or an immature to mature polymorphonuclear cell ratio greater than 0.2. (29)

Research has found that CBC values vary significantly depending on the neonate's age, arterial versus venous blood sampling, and whether the newborn is crying vigorously. (77) Normal WBC counts may be initially observed in as many as 50% of cases of culture-proven sepsis and abnormal neutrophil counts at the time of symptom onset are only observed in two thirds of neonates. (71) Newer research has shown the normal ranges for leukocyte indexes in healthy neonates with no risk factors for infection at 4 hours are considerably broader than those described in currently used reference ranges for the first 24 hours. Many researchers suggest that the immature-to-total (I:T) neutrophil ratio is the most sensitive measure. (71) However, the I:T ratio has a high interobserver variation. (81) Current research suggests that applying common reference intervals to healthy term neonates could incorrectly label large numbers as being at high risk for sepsis. (81,82)

Since 90% of EOGBSD cases are likely to present within the first 24 hours, the use of the CBC may not be as useful as recognition of clinical signs of sepsis as

an indication for treatment. (8) In one retrospective cohort study abnormal CBC values were listed as the sole indication for empiric treatment for less than 0.5% of neonates from whom a CBC had been obtained. (65) Despite recommending a CBC for the well-appearing newborn with risk factors or who has not received IAP ≥ 4 hours, the CPS guideline acknowledges that the usefulness of CBC for well-appearing infants is "conjectural" and the positive predictive value of an abnormal CBC is low. (29)

The effects of unnecessary lab evaluations were documented in a study of 242 parent-baby dyads at term, positive or unknown GBS status and no IAP or IAP < 4 hours. Researchers obtained samples for CBC, blood culture and C-reactive protein for all infants. Ten per cent of newborns had antibiotics started after initial lab values were received and 23 of 25 had antibiotics stopped after 48 hours. No newborns had a positive blood culture. (83) Subjecting asymptomatic neonates to multiple blood draws and invasive lab procedures may disrupt parent/child bonding and has limited predictive power. These results may not be generalizable to preterm neonates who received inadequate IAP. (68)

What is the best timing to obtain a CBC?

A body of studies confirms that the CBC is unreliable in the prediction of blood culture-proven GBS infection before 4 hours of life. (65,84) Current CDC recommendations suggest that the CBC take place "at birth and/or at 6-12 hours of life". (8) The CPS guideline is silent on timing of a CBC for the well-appearing infant.

SUMMARY POINTS

- Most infants with EOGBSD develop symptoms soon after birth. Rapid detection of neonatal infection and initiation of treatment is vital to minimize morbidity and mortality.
- Any neonate with clinical signs consistent with infection requires prompt treatment. Signs of sepsis in the neonate confirmed by a midwife require consultation with a paediatrician.
- Existing recommendations on the assessment and monitoring of EOGBSD, and signs that may present, are based on expert opinion and consensus.
- The incidence of clinical sepsis is likely much higher than culture-proven infection. We do not know exactly how many neonates are undergoing sepsis evaluations at a population level.
- No research was found describing parent education on monitoring for signs of sepsis or efficacy provided by midwives or other health professionals in a high resource setting, nor on the efficacy of parent monitoring for sepsis.
- Research suggests that clinical observation is sufficient for the evaluation of asymptomatic EOGBSD in at-risk neonates, and laboratory tests can cause overtreatment.
- Research suggests that hospital observation beyond 24 hours is of limited use to the well-appearing newborn who has received partial or full IAP, when risk factors are absent or present.
- In asymptomatic term neonates with risk factors, and receiving no or partial IAP, multiple studies show limited efficacy and poor yield of screening of a CBC before 4 hours after birth; expectant observation was just as effective.
- A CBC is unreliable in the prediction of blood culture-proven GBS infection before 4 hours of life; if a CBC is performed to predict EOGBSD in the well-appearing infant, it should be done once 6 to 12 hours have passed since birth. CBCs are usually done in conjunction with a blood culture.
- Available evidence suggests that close observation is a better predictor of EOGBSD in the majority of cases.

RESEARCH GAPS

- Canadian research is needed to determine the number of neonates undergoing sepsis evaluations on a population level and resulting rates of antibiotic use. More information is also needed on the rate of clinical versus culture-proven EOGBSD in Canada.
- Midwives may be unique among health care providers in the extent to which they educate and engage parents to be involved in the monitoring of their infants. There is little research available to guide midwives in preparing parents to be effectively involved in this undertaking. Further research on best practices for monitoring for signs of sepsis in the community setting is required. More research is needed on the optimal methods and timing of home-based monitoring for EOGBSD by midwives, and best practices for parent education.
- Further research is needed to develop tools for early identification of infants at risk of EOGBSD, ideally before symptoms are apparent.
- Studies of the efficacy of sepsis evaluation in the general population including low-risk and/or asymptomatic neonates are lacking; this information may be more useful to inform midwifery practice.

MANAGEMENT OF THE NEWBORN

Recommendations

1. **Midwives should review with all clients, regardless of prenatal GBS status:**

    a. **What to expect as normal newborn transition and behaviour in the first 24 hours;**
    b. **How to recognize signs in the newborn that may be indicative of sepsis (including breathing, temperature instability, colour and tone);**
    c. **How to contact the midwife and access urgent care when necessary.**

    Strong recommendation; low quality evidence.

    This recommendation recognizes that while colonization is an important risk factor for EOGBSD, sepsis may also occur in infants born to who have tested negative for GBS; it also recognizes the strengths of continuity of care and values the midwife's ability and opportunity to provide health education to parents and families.

2. **For newborns with signs of sepsis noted upon in-person exam: an immediate consult with a pediatrician (or other physician if paediatrician is unavailable) should be arranged by the midwife.**

    Strong recommendation; low quality evidence.

    This recommendation recognizes the critical outcome of EOGBSD and risks to the neonate.

3. **For asymptomatic newborns born to a client with confirmed or suspected chorioamnionitis: discuss that chorioamnionitis places the newborn at increased risk of EOGBSD regardless of whether or not IAP has been given, as well as conflicting guidance among key guideline development groups:**

    - **CDC recommendation for a limited diagnostic evaluation and antibiotic therapy pending blood culture results.**
    - **CPS recommendation that a CBC be performed and that the infant have vitals assessed q 4 hours for a period of 24 hours.**

    Midwives should consult with a paediatrician/physician to facilitate assessment/treatment for infants born to clients with chorioamnionitis.

    Strong recommendation; low quality evidence.

    This recommendation recognizes the critical outcome of EOGBSD and risks to the neonate.

4. **Management of the term infant born to a client who has screened positive for GBS:**

   a. **For all clinical situations listed below, when discussing management options for the newborn, midwives should address the following in informed choice discussions with clients:**
      i. **CDC and CPS guidelines as well as local hospital protocol applicable to the client's and newborn's clinical circumstances;**
      ii. **What is known about how risk factors, if present, may increase risks of developing EOGBSD;**
      iii. **What is known about how full, partial or no IAP may impact risk of developing EOGBSD;**
      iv. **Risks and benefits of treatment options and screening tests, as indicated, as well as choosing not to treat;**
      v. **The client's values and preferences and risk tolerance, as well as their comfort level and ability to monitor their own newborn.**

   Strong recommendation; no evidence available.

   This recommendation is based on the values of informed choice and the midwifery model of care.

   b. **Asymptomatic newborns of clients who have received IAP ≥4 hours prior to birth:**
      i. **Home observation may be recommended.**

   Strong recommendation; moderate quality evidence.

   This recommendation recognizes evidence that EOGBSD rates have been reduced following widespread IAP use.

   c. **Asymptomatic newborns of clients who have received IAP < 4 hours prior to birth (partial IAP):**
      i. **No risk factors: home observation may be recommended.**

   Weak recommendation; low quality evidence.

   This recommendation recognizes evidence that penicillin antibiotics reach bactericidal level in under 4 hours.

      ii. **PROM ≥ 18 hours or intrapartum fever ≥ 38.0°C: offer home or hospital observation.**

   Weak recommendation; low quality evidence.

   This recommendation recognizes evidence that penicillin antibiotics reach bactericidal level in less than 4 hours.

   d. **Asymptomatic newborns of clients who have not received IAP:**
      i. **No risk factors: offer home or hospital observation.**

   Weak recommendation; low quality evidence.

      ii. **PROM ≥ 18 hours or intrapartum fever ≥ 38.0°C:**
         - **Recommend hospital observation and consultation with physician for CBC and blood culture.**

   Weak recommendation; very low quality evidence.

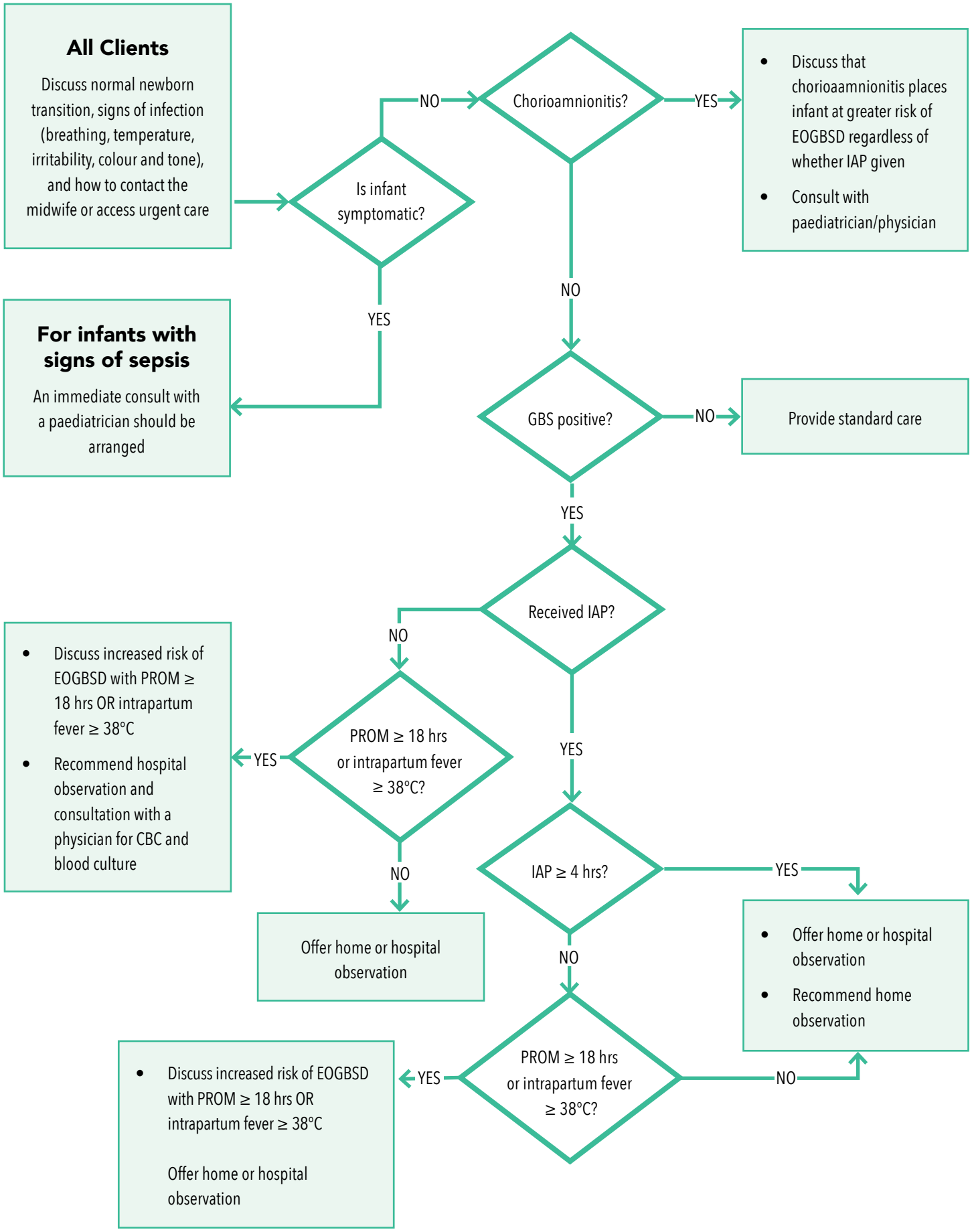
         - **Midwives may discuss the use of a CBC if client chooses home observation.**

   Weak recommendation; no evidence available.

5. **In the community setting, if a midwife determines an in-person assessment is needed to rule out EOGBSD, it should be carried out promptly with attention to distance and weather concerns.**

   Strong recommendation; no evidence available.

   This recommendation recognizes the importance of identifying sepsis in the newborn and values the skill of midwives to assess newborns in the community setting.


All Clients
Discuss normal newborn transition, signs of infection (breathing, temperature, irritability, colour and tone), and how to contact the midwife or access urgent care
Is infant symptomatic?
NO
YES
Chorioamnionitis?
YES
NO
Discuss that chorioaamnionitis places infant at greater risk of EOGBSD regardless of whether IAP given
Consult with paediatrician/physician
For infants with signs of sepsis
An immediate consult with a paediatrician should be arranged
GBS positive?
NO
Provide standard care
YES
Received IAP?
NO
YES
Discuss increased risk of EOGBSD with PROM ≥ 18 hrs OR intrapartum fever ≥ 38°C
Recommend hospital observation and consultation with a physician for CBC and blood culture
PROM ≥ 18 hrs or intrapartum fever ≥ 38°C?
YES
NO
Offer home or hospital observation
IAP ≥ 4 hrs?
YES
NO
Offer home or hospital observation
Recommend home observation
PROM ≥ 18 hrs or intrapartum fever ≥ 38°C?
YES
NO
Discuss increased risk of EOGBSD with PROM ≥ 18 hrs OR intrapartum fever ≥ 38°C
Offer home or hospital observation

The near-term neonate

Since midwives will maintain primary care of the well, near-term neonate (≥ 34 weeks' gestation), following a consultation with a physician, research relating to the incidence and etiology of EOGBSD this population is relevant. The near-term neonate is more likely to face challenges with thermoregulation, feeding difficulties and poor immunological and respiratory defence systems. (85) One UK case review of both early onset (N=377) and late onset GBS disease (N=191) found increased mortality rates for both early and late infection in preterm (15.2% at ≤ 33 weeks' GA) and near-term infants (13.2% at 34-36 weeks' GA) compared with term infants (6.4% at ≥ 37 weeks' GA). The overall mortality rate in this study was 9.7% and the overall incidence of EOGBSD in this population was 0.48/1000 births. (86)

Near-term neonates are not uniformly defined in research studies. Two prospective cohort studies were found examining the incidence of sepsis evaluation and proven sepsis in the near-term neonate. Of 1233 near-term NICU admissions from 2000-2004 from a single site, 6 (4.9/1000) had culture-proven EOGBSD. Because the signs can be subtle or mimic other medical conditions (hypoglycemia, delayed transition, transient tachypnea of the newborn), diagnosis of EOS in the near-term neonate is challenging. This may result in many near-term neonates being evaluated for sepsis, and receiving empiric antibiotics. (87)

In another prospective cohort study of 119 130 neonates < 3 days old born at 34 to 36 weeks' gestational age, there were 6/1000 cases of EOS caused by any organism. No deaths were associated with GBS. Twenty-nine per cent of near-term neonates with EOS were exposed to IAP. The proportion of near-term neonates that were evaluated for sepsis in the first 3 days was 69%, compared to a rate of only 0.4% confirmed cases. (88) The relatively low rate of proven EOS versus the number of near-term neonates being evaluated for sepsis suggests a high rate of unnecessary intervention may be taking place in this population.

The CPS recommends that well-appearing infants born between 34 to 36^{+6} weeks' GA whose GBS status is unknown and did not receive IAP should receive a limited diagnostic evaluation and not be discharged before 48 hours. (29) Because near-term infants are at an increased risk of infection, parents should be taught the importance of hand washing and cautioned to avoid newborn exposure to individuals with upper respiratory tract infections. (85)

SUMMARY POINTS

- Limited evidence shows that near-term neonates undergo sepsis evaluations at a much higher rate than term neonates, despite a low absolute rate of proven sepsis.
- Limited evidence suggests that near-term infants who develop EOGBSD have higher mortality rates than term infants, but lower mortality rates than preterm infants. For 34 to 36^{+6} week old neonates who are well-appearing, whose GBS status is unknown and did not receive IAP, the CPS recommends a limited diagnostic evaluation (CBC and q 4 hours observation for 24 hours). The CPS does not recommend discharge prior to 48 hours. (29) If the neonate has received full IAP, the CPS recommends routine neonatal care. The CPS further advises that discharge plans should consider health of the neonate as well as parenting and feeding skills. (85)

CONCLUSION

The incidence of EOGBSD in Canada and the U.S. has declined significantly since the introduction of universal screening for maternal colonization of GBS and IAP. (8) It is estimated that widespread GBS screening and use of IAP has reduced the incidence of EOGBSD by approximately 80%. (18,89) Evidence suggests that the bactericidal effects of prophylactic antibiotics are achieved soon after administration, though researchers have not determined the extent to which EOGBSD morbidity and mortality is reduced with durations of IAP < 4 hours.

EOGBSD is a rare disease associated with morbidity and mortality. This combination of characteristics presents particular challenge to maternity care providers and parents interested in minimizing unnecessary intervention. It is acknowledged that neonatal sepsis is over-evaluated and over-treated. (80) Some of this over-evaluation may be unavoidable: clinical signs are varied and non-specific and risk of disability or death increases with delayed treatment. Since tests for sepsis are protracted and are not particularly definitive, clinicians may suggest treatment while results are pending or regardless of their eventual outcome. Canadian research is needed to determine the number of neonates undergoing sepsis evaluations on a population level and resulting rates of antibiotic use. More information is also needed on the rate of clinical versus culture-proven EOGBSD in Canada.

Existing knowledge on the best approach to assessment and monitoring of EOGBSD is based on expert opinion and consensus. Researchers' attempts to create predictive models based on intrapartum or neonatal risk factors are made difficult by the unpredictable onset of EOGBSD and the available literature suggests that clinical observation is largely sufficient for purposes of evaluation. Midwives may be unique among health care providers in the extent to which they educate and engage parents to be involved in the monitoring of their infants. While there is little research available to guide midwives in preparing parents to be effectively involved in this undertaking, home observation of the asymptomatic newborn is a reasonable option which may be encouraged. More research is needed on the optimal methods and timing of home-based monitoring for EOGBSD by midwives, and best practices for parent education.

RECOMMENDATIONS: MANAGEMENT OF THE NEWBORN

1. **Midwives should review with all clients, regardless of prenatal GBS status:**

    a. **What to expect as normal newborn transition and behaviour in the first 24 hours;**
    b. **How to recognize signs in the newborn that may be indicative of sepsis (including breathing, temperature instability, colour and tone);**
    c. **How to contact the midwife and access urgent care when necessary.**

    Strong recommendation; low quality evidence.

    This recommendation recognizes that while colonization is an important risk factor for EOGBSD, sepsis may also occur in infants born to those who have tested negative for GBS; it also recognizes the strengths of continuity of care and values the midwife's ability and opportunity to provide health education to parents and families.

2. **For newborns with signs of sepsis noted upon in-person exam: an immediate consult with a paediatrician (or other physician if paediatrician is unavailable) should be arranged by the midwife.**

    Strong recommendation; low quality evidence.

    This recommendation recognizes the critical outcome of EOGBSD and risks to the neonate.

3. **For asymptomatic newborns born to a client with confirmed or suspected chorioamnionitis: discuss that chorioamnionitis places the newborn at increased risk of EOGBSD regardless of maternal GBS status and whether or not IAP has been given, as well as conflicting guidance among key guideline development groups:**

    - **CDC recommendation for a limited diagnostic evaluation and antibiotic therapy pending blood culture results.**
    - **CPS recommendation that a CBC be performed and that the infant have vitals assessed q 4 hours for a period of 24 hours.**

    Midwives should consult with a paediatrician/physician to facilitate assessment/treatment for infants born to clients with chorioamnionitis.

    Strong recommendation; low quality evidence.

    This recommendation recognizes the critical outcome of EOGBSD and risks to the neonate.

4. **Management of the term infant born to a client who has screened positive for GBS:**

    a. **For all clinical situations listed below, when discussing management options for the newborn, midwives should address the following in informed choice discussions with clients:**
        i. **CDC and CPS guidelines as well as local hospital protocol applicable to the client's and newborn's clinical circumstances;**
        ii. **What is known about how risk factors, if present, may increase risks of developing EOGBSD;**
        iii. **What is known about how full, partial or no IAP may impact risk of developing EOGBSD;**
        iv. **Risks and benefits of treatment options and screening tests, as indicated, as well as choosing not to treat;**
        v. **The client's values and preferences and risk tolerance, as well as their comfort level and ability to monitor their own newborn.**

    Strong recommendation; no evidence available.

    This recommendation is based on the values of informed choice and the midwifery model of care.

RECOMMENDATIONS: MANAGEMENT OF THE NEWBORN

b. Asymptomatic newborns of clients who have received IAP ≥4 hours prior to birth:
   i. Home observation may be recommended.

Strong recommendation; moderate quality evidence.

This recommendation recognizes evidence that EOGBSD rates have been reduced following widespread IAP use.

c. Asymptomatic newborns of clients who have received IAP < 4 hours prior to birth (partial IAP):
   i. No risk factors: home observation may be recommended.

Weak recommendation; low quality evidence.

This recommendation recognizes evidence that penicillin antibiotics reach bactericidal level in under 4 hours.

   ii. PROM ≥ 18 hours or intrapartum fever ≥ 38.0°C: offer home or hospital observation.

Weak recommendation; low quality evidence.

This recommendation recognizes evidence that penicillin antibiotics reach bactericidal level in less than 4 hours.

d. Asymptomatic newborns of clients who have not received IAP:
   i. No risk factors: offer home or hospital observation.

Weak recommendation; low quality evidence.

   ii. PROM ≥ 18 hours or intrapartum fever ≥ 38.0°C:
   - Recommend hospital observation and consultation with physician for CBC and blood culture.

Weak recommendation; very low quality evidence.

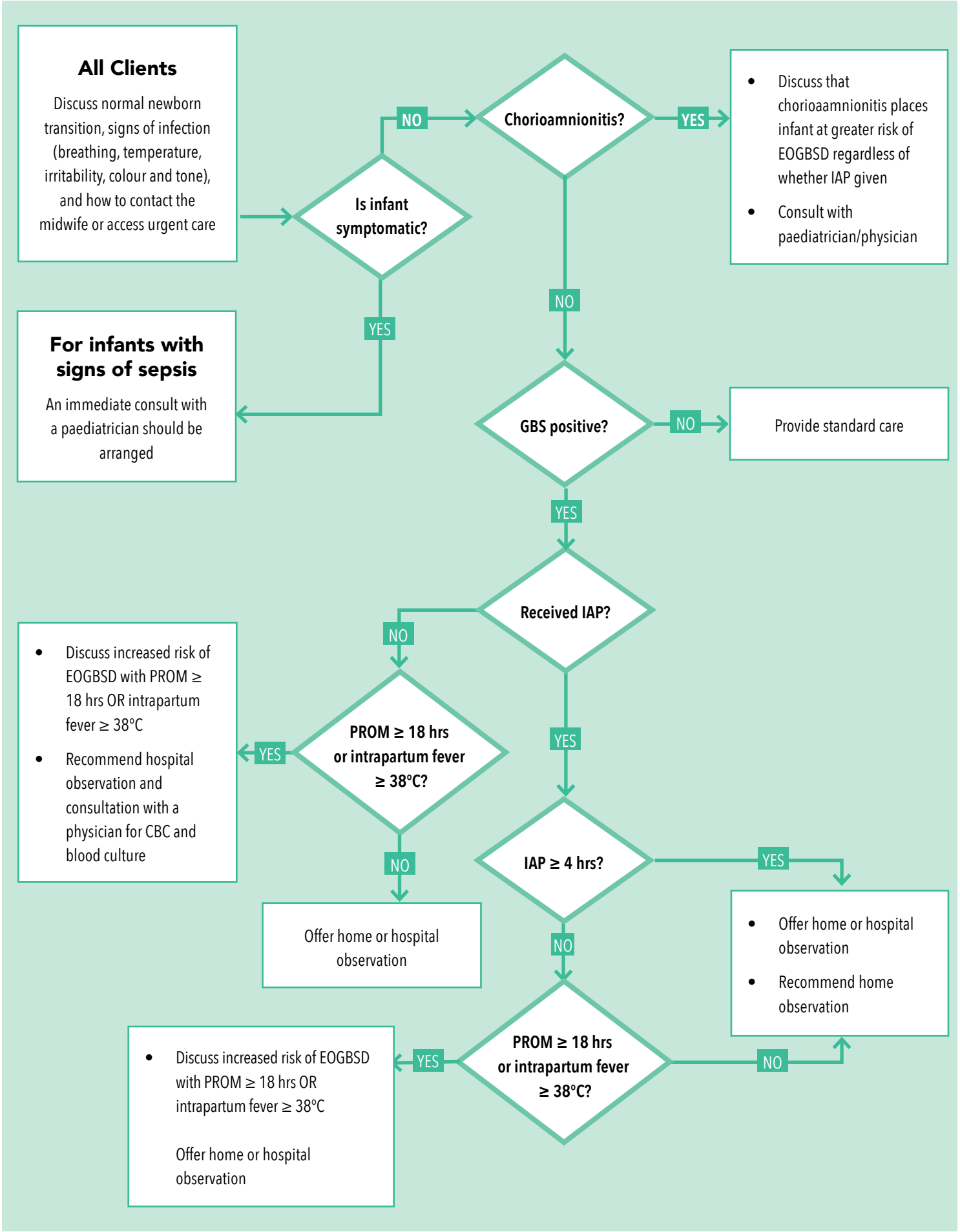
   - Midwives may discuss the use of a CBC if client chooses home observation.

Weak recommendation; no evidence available.

5. In the community setting, if a midwife determines an in-person assessment is needed to rule out EOGBSD, it should be carried out promptly with attention to distance and weather concerns.

Strong recommendation; no evidence available.

This recommendation recognizes the importance of identifying sepsis in the newborn and values the skill of midwives to assess newborns in the community setting.


All Clients
Discuss normal newborn transition, signs of infection (breathing, temperature, irritability, colour and tone), and how to contact the midwife or access urgent care
Is infant symptomatic?
NO
YES
Chorioamnionitis?
NO
YES
Discuss that chorioaamnionitis places infant at greater risk of EOGBSD regardless of whether IAP given
Consult with paediatrician/physician
For infants with signs of sepsis
An immediate consult with a paediatrician should be arranged
GBS positive?
NO
Provide standard care
YES
Received IAP?
NO
YES
Discuss increased risk of EOGBSD with PROM ≥ 18 hrs OR intrapartum fever ≥ 38°C
Recommend hospital observation and consultation with a physician for CBC and blood culture
PROM ≥ 18 hrs or intrapartum fever ≥ 38°C?
YES
NO
Offer home or hospital observation
IAP ≥ 4 hrs?
YES
NO
Offer home or hospital observation
Recommend home observation
PROM ≥ 18 hrs or intrapartum fever ≥ 38°C?
YES
NO
Discuss increased risk of EOGBSD with PROM ≥ 18 hrs OR intrapartum fever ≥ 38°C
Offer home or hospital observation

APPENDICES

Appendix 1: Interpreting GRADE recommendations: Canadian Task Force on Preventative Health Care

G R A D E

GRADES OF RECOMMENDATION, ASSESSMENT, DEVELOPMENT, AND EVALUATION

TARGET AUDIENCE	STRONG RECOMMENDATION	WEAK RECOMMENDATION
FOR PATIENTS/ PUBLIC	We believe most people in this situation would want the recommended course of action and only a small number would not.	We believe that most people in this situation would want the recommended course of action, but many would not. Different choices are acceptable for each person and clinicians should support patients and discuss their values and preferences to reach a decision. Decision aids may support people in reaching these decisions.
FOR CLINICIANS	The recommendation would apply to most individuals. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	We recognize that different choices may be appropriate for individual patients. Clinicians should support each patient in reaching a management decision consistent with his or her values and preferences. Decision aids may support individuals in reaching such decisions.
FOR POLICY MAKERS AND DEVELOPERS OF QUALITY MEASURES	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Policy-making will require substantial debate and involvement of various stakeholders. An appropriately documented decision making process could be used as quality indicator.

SOURCE: Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group, 2011.

This companion document to Task Force recommendations is also available on the Canadian Task Force on Preventive Health Care's website at **www.canadiantaskforce.ca**

Quality of Evidence

Recommendations in the guidelines prepared by the Canadian Task Force on Preventive Health Care (CTFPHC) www.canadiantaskforce.ca are graded as either strong or weak according to the Grading of Recommendations Assessment, Development and Evaluation system (GRADE). The CTFPHC's judgments about the **quality of evidence** are summarized by the degree of confidence that available evidence correctly reflects the theoretical true effect of the intervention or service.

We judge evidence as **high quality** when we are highly confident that the true effect lies close to that of the estimate of the effect. For example, evidence is judged as high quality if all of the following apply: there is a wide range of studies included in the analyses with no major limitations, there is little variation between studies, and the summary estimate has a narrow confidence interval.

We judge evidence as **moderate quality** when we consider that the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. For example, evidence might be judged as moderate quality if any of the following applies: there are only a few studies and some have limitations but not major flaws, there is some variation between studies, or the confidence interval of the summary estimate is wide.

We judge evidence to be **low or very low quality** when the true effect may be substantially different from the estimate of the effect. For example, evidence might be judged as low quality if any of the following applies: the studies have major flaws, there is important variation between studies, or the confidence interval of the summary estimate is very wide.

Strength of Recommendations

In addition to the quality of supporting evidence, **the strength of our recommendations** is influenced by,

- the balance between desirable and undesirable effects;
- the variability or uncertainty in values and preferences of citizens; and
- whether or not the intervention represents a wise use of resources.

Strong recommendations are those for which **we are confident** that the desirable effects of an intervention outweigh its undesirable effects (strong recommendation for an intervention) **or** that the undesirable effects of an intervention outweigh its desirable effects (strong recommendation against an intervention). A strong recommendation implies that most individuals will be best served by the recommended course of action.

Weak recommendations are those for which the desirable effects **probably** outweigh the undesirable effects (weak recommendation for an intervention) **or** undesirable effects probably outweigh the desirable effects (weak recommendation against an intervention) but uncertainty exists. Weak recommendations result when the balance between desirable and undesirable effects is small, the quality of evidence is lower, and there is more variability in the values and preferences of individuals. A weak recommendation implies that we believe most people would want the recommended course of action but that many would not. Clinicians must recognize that different choices will be appropriate for different individuals, and they must support each person in reaching a management decision consistent with his/her values and preferences. Policy-making will require substantial debate and involvement of various stakeholders.

SOURCE: Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group, 2011.

This companion document to Task Force recommendations is also available on the Canadian Task Force on Preventive Health Care's website at
www.canadiantaskforce.ca

Appendix 2: Indications for GBS prophylaxis

Universal screening strategy

This is the strategy currently endorsed by the CDC and the SOGC. (8,9)

Indications for IAP according to a universal screening strategy:

- Positive GBS screening at 35 to 37 weeks' gestation
  - OR • Previous infant infected with GBS, regardless of GBS status in current pregnancy
  - OR • Documented GBS bacteriuria (regardless of level of colony-forming units per mL) in this pregnancy
  - OR • GBS-unknown clients with 1 or more of the following risk factors:
    - o preterm labour < 37 weeks' gestation
    - o rupture of membranes ≥ 18 h
    - o intrapartum maternal fever ≥ 38°C

Predicted outcomes of a universal screening strategy:		Source:
Proportion of clients predicted to receive IAP	31%	(90)
Theoretical reduction in EOGBSD	65% to 86%	(90)
NNT with IAP to prevent one case of EOGBSD	1000 to 2000	(91,92)

Risk factor-only strategy

Prior to the publication of the CDC's 2002 guidelines, the CDC and SOGC considered this strategy to be a suitable alternative to the universal screening approach. (93,94) The CDC's recommendations were revised following the publication of a large retrospective cohort study that found statistically significantly lower rates of EOGBSD in individuals who underwent universal screening (RR 0.46, 95% CI 0.36-0.60) compared to treatment based on risk factors alone . (90)

Indications for IAP according to a risk factor-only strategy:

- Presence of 1 or more of the following risk factors
  - o preterm labour < 37 weeks' gestation
  - o rupture of membranes ≥ 18 h
  - o intrapartum fever ≥ 38°C
  - OR • Documented GBS bacteriuria (regardless of level of colony-forming units per mL) in current pregnancy
  - OR • Previous infant infected with GBS, regardless of GBS status in current pregnancy

Predicted outcomes of a risk factor-only strategy:		Source:
Proportion of clients predicted to receive IAP	29%	(90)
Theoretical reduction in EOGBSD	39% to 53%	(95)
NNT with IAP to prevent one case of EOGBSD	~1000	(92)

Screening with risk factors strategy

The AOM suggests offering this alternative strategy along with the option of a universal screening strategy to clients as part of their informed choice discussion regarding GBS. (20) This approach is suggested by the Canadian Task Force on Preventive Health Care as well as the authors of a Cochrane Review on intrapartum antibiotics for known maternal GBS colonization. (91,96)

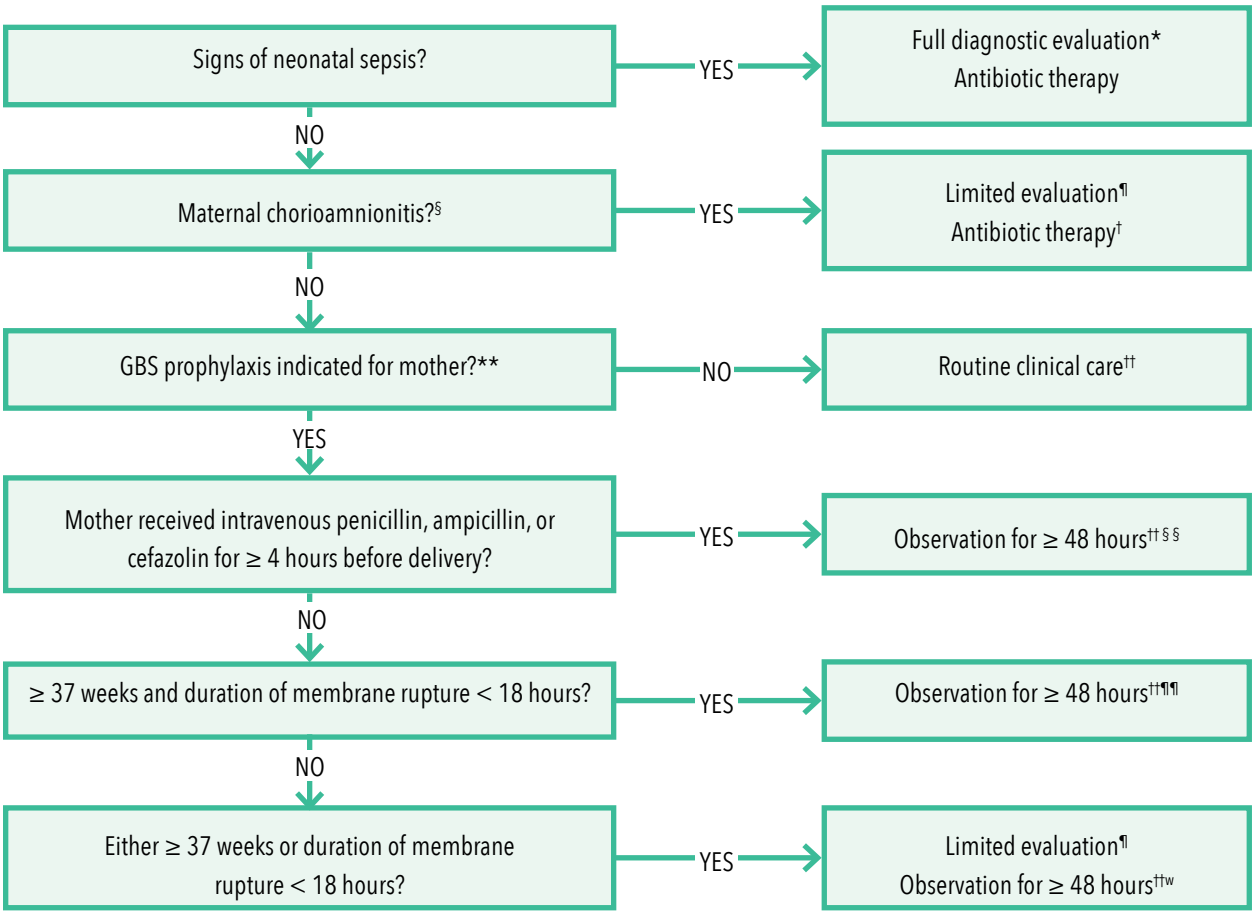
Indications for IAP according to a screening with risk factors strategy:

- Positive GBS screening at 35 to 37 weeks'
  AND 1 or more of the following risk factors:
    - preterm labour < 37 weeks' gestation
    - rupture of membranes ≥ 18 h
    - intrapartum fever ≥ 38°C
  OR • Previous infant infected with GBS, regardless of GBS status in current pregnancy
  OR • Documented GBS bacteriuria (regardless of level of colony-forming units per mL) in this pregnancy

Predicted outcomes of a screening with risk factors strategy:		Source:
Proportion of clients predicted to receive IAP	3.4% to 6%	(90,91,97)
Theoretical reduction in EOGBSD	51% to 75%	(70,98)
NNT with IAP to prevent one case of EOGBSD	6	(91)

Appendix 3 Neonatal care pathways: CDC and CPS

Centers for Disease Control and Prevention 2010 Recommendations



* 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 full CDC guideline for indications for intrapartum GBS prophylaxis.

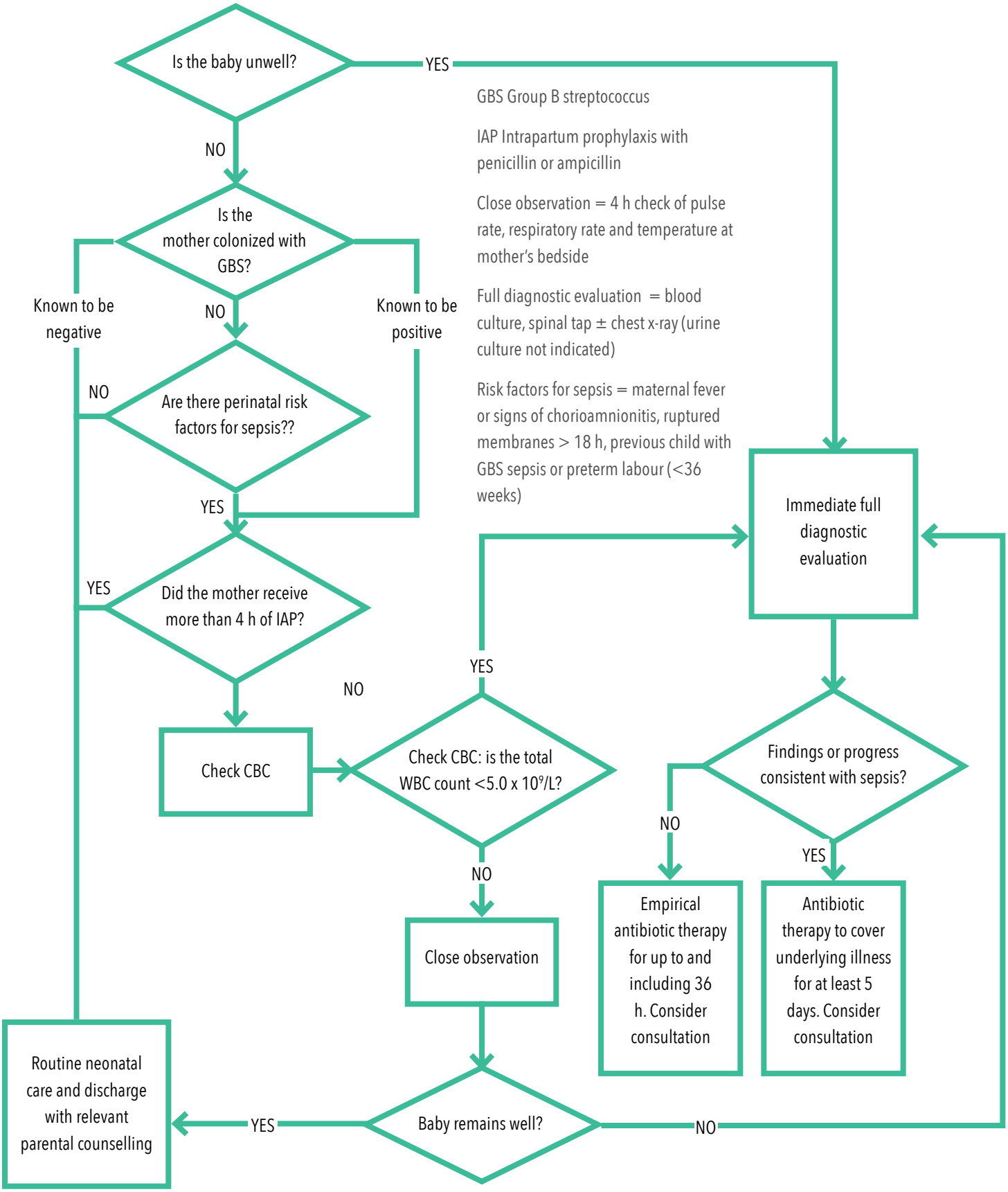
†† If signs of sepsis develop, a full diagnostic evaluation should be conducted and antibiotic therapy initiated.

§§ 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.

Canadian Paediatric Society 2007 Recommendations

(29)



Online Appendix: GRADE Tables

Three of the research questions developed to guide AOM Clinical Practice Guideline No. 16 – *Group B Streptococcus: Postpartum Management of the Neonate* addressed clinical findings that could be summarized in GRADE quality of evidence and summary of findings tables.

The full clinical practice guideline is available at: http://www.aom.on.ca/Health_Care_Professionals/

Question: Should vaginal chlorhexidine versus placebo or no treatment be used for EOGBSD? [1,2]

Sources: (1)

Quality Assessment							Summary of Findings				
Participants (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates** (%)		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With placebo or no treatment	**With vaginal chlorhexadine**		**Risk with placebo or no treatment**	**Risk difference with vaginal chlorhexadine** (95% CI)
GBS sepsis within first 7 days											
987 (2 studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊕ **HIGH**	1/536 (0.19%)	2/451 (0.44%)	**RR 2.32** (0.34 to 15.63)	**2 per 1000**	**2 more per 1000** (from 1 fewer to 27 more)
GBS pneumonia within first 7 days											
987 (2 studies)	no serious risk of bias	no serious inconsistency	serious[3]	no serious imprecision	undetected	⊕⊕⊕⊖ **MODERATE**[3] due to indirectness	1/536 (0.19%)	0/451 (0%)	**RR 0.35** (0.01 to 8.6)	**2 per 1000**	**1 fewer per 1000** (from 2 fewer to 14 more)

GBS meningitis within the first 7 days											
1066 (3 studies)	no serious risk of bias	no serious inconsistency	serious[4]	no serious imprecision	undetected	⊕⊕⊕⊖ **MODERATE**[4] due to indirectness	1/578 (0.17%)	0/488 (0%)	**RR 0.35** (0.01 to 8.6)	**2 per 1000**	**1 fewer per 1000** (from 2 fewer to 13 more)
Neonatal colonization with GBS within first 7 days											
328 (3 studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊕ **HIGH**	115/200 (57.5%)	48/128 (37.5%)	**RR 0.72** (0.56 to 0.91)[5]	**575 per 1000**	**161 fewer per 1000** (from 52 fewer to 253 fewer)
Mortality due to EOGBSD											
269 (2 studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	See comment	0/169 (0%)	0/100 (0%)	Cannot calculate	Cannot calculate	Cannot calculate
Adverse effects in the mother (assessed with: self-report by women, stinging or local irritation)											
2131 (5 studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊕ **HIGH**	10/1122 (0.89%)	18/1009 (1.8%)	**RR 1.88** (0.9 to 3.96)	**9 per 1000**	**8 more per 1000** (from 1 fewer to 26 more)

[1] No study compared impact of mechanical washing with chlorhexidine on GBS morbidity, compared to mechanical washing with placebo.

[2] Only GBS+ women were considered in the systematic review.

[3] Lack of clarity in defining outcomes: GBS septicemia and GBS meningitis.

[4] Lack of clarity in defining outcomes: GBS septicemia and GBS meningitis.

[5] Number needed to benefit = 6 (95% CI 4 - 20).

Question: Should CBC and blood culture be used in asymptomatic newborns?

Sources: (2-8)

Quality Assessment							Summary of Findings				
Studies		**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates** (%)		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With placebo or no treatment	**With vaginal chlorhexadine**		**Risk with placebo or no treatment**	**Risk difference with vaginal chlorhexadine** (95% CI)
Abnormal CBC											
7 studies	no serious risk of bias	serious[1]	serious[2]	no serious imprecision	undetected	⨁□□□ VERY LOW	n/a	n/a	n/a	n/a	n/a

[1] Outcomes were measured inconsistently (i.e. by blood culture, clinical signs, CBC at varying times after birth).

[2] Different populations were used in different studies. Some were limited to only confirmed cases of EOGBSD, while others included all neonates with signs of early onset disease, or all neonates ever evaluated for sepsis.

Question: Should IAP < 4 hours versus no IAP be used for GBS prophylaxis?

Sources: (9-11)

Quality Assessment							Summary of Findings		
Participants (studies)	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**No. of patients**		**Quality**
							IAP < 4 hours	**No IAP**	
GBS colonization[1] (assessed with: neonatal GBS colonization at > 10 hours at mucosal sites)									
167 (2 studies)	observational studies	no serious risk of bias	no serious inconsistency	serious	no serious imprecision[2]	dose response gradient[3]	5/137 (3.6%)	18/30 (60%)	⊕⊕◯◯ LOW
Fetal serum levels of penicillin G (measured with: fetal cord blood)									
98 (1 study)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[4]	dose response gradient[5]	57/98	-	⊕⊕◯◯ LOW
Concentration of ampicillin in amniotic fluid (measured with: amniocentesis just prior to ECS)									
40 (1 study)	observational studies	no serious risk of bias	no serious inconsistency	serious[6]	no serious imprecision	dose response gradient[7]	40/40	-	⊕⊕◯◯ LOW

[1] Only study to exclude all mothers with other risk factors for EOGBSD.

[2] Mothers were cultured within 48 hours of delivery to confirm GBS carriage.

[3] Somewhat, 1/2 the rate of colonization at 24 hours with IAP > 2 < 4 hours versus ≤ 2 hours. But very small numbers (2 versus 1 newborns).

[4] No cases of EOGBSD (clinical or proven).

[5] The highest value of penicillin G concentration in the cord blood was observed at approximately 1 hour after administration of the loading dose of 5 million units. All groups achieved penicillin G levels significantly above the minimum inhibitory concentration for GBS (0.1 μg/mL), p < .002. Furthermore, penicillin G levels observed in each individual cord blood sample were 10- to 179-fold above the MIC.

[6] No labour, GBS status unknown.

[7] Ampicillin levels in the amniotic fluid exceeded the lower threshold of the minimum inhibitory concentrations in 28 of 33 (85%) of the specimens (administered between 3 and 67 minutes).

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