

**TEXAS CHILDREN'S HOSPITAL**  
**EVIDENCE-BASED OUTCOMES CENTER**  
**Managing Postpartum Hypertension**  
Evidence-Based Medicine Course Evidence Summary

**Inclusion Criteria**

- Women of child-bearing age, hospitalized during the postpartum period following vaginal or Cesarean delivery

**Exclusion Criteria**

- Patients on longstanding antihypertensive agent

**Background**

Hypertension during pregnancy affects 10% of all pregnancies. <sup>(1)</sup> It is associated with increased perinatal morbidity and mortality and is the second leading cause of maternal death in the world. <sup>(2)</sup> Preeclampsia/Eclampsia represent the most severe of hypertensive disorders of pregnancy, and indeed the leading cause of death in women with preeclampsia is cerebral hemorrhage secondary to uncontrolled hypertension. <sup>(3,4)</sup> During the postpartum period the return of fluid from the interstitial and extravascular compartments to intravascular space can lead to elevated blood pressures and the persistence can lead to increased morbidity. <sup>(5)</sup> New onset PPHTN can occur with frequency ranging from 0.3% to 27.5 %, and lead to complications such as stroke, eclampsia, and death. <sup>(6,7)</sup> In these women, maternal and fetal risks may be decreased by lowering of blood pressure to safer levels with anti-hypertensive drugs.

Although there has been extensive study on "classic" or antepartum preeclampsia, there is a relative lack of information about "late" or delayed postpartum preeclampsia (LPP). Preeclampsia (preE) is a clinical syndrome of pregnancy considered to be rooted in endothelial dysfunction, and which presents in a wide range of severity, ranging from mild proteinuria and hypertension to very severe form of rapid, fulminant disease with multi organ failure, seizure, and death. <sup>(8)</sup> The historical understanding is that fetal delivery is the definitive treatment for preeclampsia. However, there is growing recognition of a spectrum of preeclampsia that can occur despite fetal delivery, during the postpartum period. An early 2004 case series of 151 patients by Matthys, et al. showed that delivery does not eliminate the risk for preeclampsia and its complications. <sup>(9)</sup> Furthermore, Filetti, et al. have shown that LPP can occur *de novo*, without antecedent syndrome prior to delivery, and otherwise sharing similar clinical course and complications. <sup>(10)</sup>

Despite the growing recognition of LPP as an entity, there remain unanswered questions about the management of patients with postpartum hypertension (PPHTN) as it relates to the LPP. For instance, transient PPHTN is common in the immediate postpartum period and is likely secondary to physiologic shifts in cardiovascular and endocrine physiology following normal delivery. <sup>(5)</sup> Yet, as preeclampsia is a clinical diagnosis, any elevated blood pressure readings associated with headache, visual disturbance, edema or laboratory abnormalities may lead to a diagnosis of LPP and result in postpartum hospital readmission. Thus, there is interest in both developing more robust diagnostic criteria for LPP, as well as analyzing hospital readmissions for risk factors that may predict occurrence of PPHTN/LPP.

**Critically Analyze the Evidence**

The **GRADE criteria** were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. The table below defines how the quality of evidence is rated and how a strong versus a weak recommendation is established.

Recommendation	
<b>STRONG</b>	Desirable effects clearly outweigh undesirable effects or vice versa
<b>WEAK</b>	Desirable effects closely balanced with undesirable effects
Quality	Type of Evidence
<b>High</b>	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies
<b>Moderate</b>	Evidence from RCTs with important limitations (e.g., inconsistent results, methodological flaws, indirect evidence, or imprecise results) or unusually strong evidence from unbiased observational studies
<b>Low</b>	Evidence for at least 1 critical outcome from observational studies, from RCTs with serious flaws or indirect evidence
<b>Very Low</b>	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence

**PICO Question 1:** In inpatient postpartum women without preeclampsia during incident pregnancy, can risk factors predict incidence of symptomatic postpartum hypertension or hospital readmission for de novo postpartum preeclampsia?

**Recommendation(s):**

Consider screening for risk factors of late onset preeclampsia (antenatal hypertensive disease, Cesarean section delivery, >40 years old, African American ethnicity, Latino, BMI  $\geq 30$  and gestational diabetes) and provide patient education. (5,8-13) – Weak recommendation, low quality evidence

Consider screening for risk factors of late onset preeclampsia (antenatal hypertensive disease, Cesarean section delivery, >40 years old, African American ethnicity, Latino, BMI  $\geq 30$  and gestational diabetes) and plan earlier follow up. (5,8-13) – Weak recommendation, low quality evidence

The first evaluated study, a retrospective case control study by Bigelow, et al., was the first study to examine risk factors in the development of de novo postpartum preeclampsia. Logistic regression models on a small number ( $n = 34$ ) of women diagnosed with de novo LPP showed that age  $\geq 40$  years old, African American or Latino race, final pregnancy BMI  $\geq 30$ , and gestational diabetes mellitus were predictive for de novo onset. The sensitivity and specificity of having  $\geq 1$  of these characteristics was 100% and 59%, and the sensitivity and specificity of having  $\geq 2$  was 56 and 93%. (11) Although these are novel findings, the generalizability of these findings is limited due to the small sample size and limited sampling from a single American tertiary care center.

The second evaluated study is a recent (2015) retrospective study by Goel, et al. that investigated risk factors for development of de novo postpartum hypertension (PPHTN) following Cesarean deliveries. (12) They found a 10% incidence of de novo PPHTN, with logistic regression showing higher BMI ( $30 \pm 5$  kg/m<sup>2</sup> vs.  $24 \pm 7$  kg/m<sup>2</sup>), African American race (21% vs. 7%), and diabetes mellitus (13% vs. 4%) as predictive risk factors with all  $p < 0.001$ . A higher, although within normal range, antepartum blood pressure was also associated with later development of de novo PPHTN (SBP,  $127 \pm 8$  mmHg vs.  $119 \pm 11$  mmHg; DBP  $78 \pm 7$  mmHg vs.  $74 \pm 8$  mmHg; all  $p < 0.001$ ). The generalizability of these findings is also limited due to the limited sampling and inclusion of strictly post-Cesarean section subjects.

One study of postpartum readmissions for preeclampsia by Larsen was included, which included a large number (39%) of patients with antecedent preeclampsia. This study was included because the majority of patients (61%) presumably had de novo LPP, and also for the purpose of comparison with the more contemporary studies specific to de novo LPP. Logistic regression analysis of readmissions occurring between 48 hours and 4 weeks postpartum showed that the following variables were predictive of postpartum preeclampsia: BMI  $\geq 30$ , African American race, Cesarean delivery, hypertensive disorder during incident pregnancy (AUC for receiver operator curve 0.896). Patient age, history of preeclampsia on prior pregnancy were not significant. Asian ethnicity was protective (6% vs. 22%; OR 0.22; 95% CI: 0.06 - 0.8;  $p = 0.01$ ). (13)

**PICO Question 2:** In postpartum women, does early initiation of pharmacologic antihypertensive therapy for mildly elevated blood pressure reduce the subsequent incidence or hospitalization rate for symptomatic postpartum hypertension or preeclampsia?

**Recommendation(s):** Unable to make a recommendation due to lack of evidence.

**PICO Question 3:** In women without preeclampsia during incident pregnancy, does close follow-up following hospital discharge for those at increased risk for postpartum hypertension impact subsequent hospitalization rate for symptomatic postpartum hypertension or preeclampsia?

**Recommendation(s):** Unable to make a recommendation due to lack of evidence.

**PICO Question 4:** In inpatient postpartum women with mild/moderate hypertension, is oral nifedipine more effective than labetalol for blood pressure control?

**Recommendation(s):**

For the treatment of acute postpartum hypertension, defined as consistent SBP  $\geq 160$  and/or DBP  $\geq 105$ -110 mmHg, oral nifedipine 10 mg is a safe and effective pharmacologic option. – Strong recommendation, low quality evidence

For the treatment of acute postpartum hypertension, defined as consistent SBP  $\geq 160$  and/or DBP  $\geq 105$ -110 mmHg, oral nifedipine is as effective as intravenous labetalol of equivalent dosing. – Strong recommendation, low quality evidence

IV labetalol is as efficacious as oral nifedipine for treatment of acute peripartum/postpartum hypertension; however, oral nifedipine may provide additional benefits such as faster blood pressure control, increased urinary output and cardiac index. Additionally, the oral route of administration is preferred to IV during the postpartum period. There were no data found comparing nifedipine to labetalol for mild to moderate hypertension during postpartum period.

Most authorities recommend nifedipine, labetalol, or hydralazine as first line treatments for severe hypertension during pregnancy. (14) Still, as noted by Shekhar, et al., there is a need for larger powered trials comparing oral nifedipine and IV labetalol for treatment of severe hypertension during pregnancy. (15) The Cochrane review on the topic concluded that, until better evidence is available, the choice of antihypertensive therapy should depend on provider judgment and familiarity. (16) The 2010 UK National Institute for Health and Clinical Excellence Hypertension and Pregnancy guideline recommends oral nifedipine or labetalol in women during pregnancy or after birth for treatment of severe hypertension. (17) Both labetalol and nifedipine are commonly prescribed during the postpartum period as they are compatible with breastfeeding. There are no studies comparing oral nifedipine and labetalol for mild to moderate hypertension during the postpartum period, but a literature search did find several studies comparing the two pharmacotherapies for severe hypertension during the postpartum period. There are several clinical trials going on right now regarding treatment for postpartum hypertension. Two trials are specifically comparing labetalol vs. procordia to determine if one is superior to the

other at management of postpartum severe hypertension, the time to achieve goal blood pressure, and hospital stay. One study is looking at procordia tablets vs. labetalol tablets and the other procordia extended release tables vs. labetalol tablets.

In 1999, Vermillion used a randomized double-blinded trial to compare the efficacy of oral nifedipine versus intravenous labetalol for control of acute hypertensive emergencies in pregnancy. Although there was no significant difference in efficacy of blood pressure control, nifedipine had a significantly shorter time to achieve blood pressure control (25 min.  $\pm$  SD 13.5 min. and 43.6 min.  $\pm$  25.4 min.;  $p = 0.002$ ). A secondary finding was that treatment with nifedipine resulted in significantly increased urine output compared to labetalol at 1 hour (99 ml  $\pm$  99 mL, and 44.8  $\pm$  19.1 mL) and remained significantly increased at 2, 6, 12, 18, 24 hours after initial administration. Vermillion, et al. conclude that although oral nifedipine and intravenous labetalol similarly effective for blood pressure control during pregnancy, nifedipine offers more rapid control and is associated with favorable secondary outcomes such as increased urine output. Nifedipine's effect to increase renal perfusion may be of particular benefit in patients with preeclampsia, which can cause a state of intravascular volume and decreased renal perfusion. Limitations of this study include co-administration of intravenous magnesium sulfate (Mg-S) in all subjects for seizure prophylaxis. Additionally, this study compared drug regimens intended for management of acute hypertension, and do not inform the administration of maintenance dosages. <sup>(18)</sup> Lastly, the sample size was based on the primary outcome of time to achieve blood pressure control, and not to prove safety of either medication.

Two other similar double blind randomized trials by Raheem and Shekhar compared oral nifedipine versus intravenous labetalol for treatment of hypertension in pregnant women to quickly and safely achieve target blood pressure <150/100 mmHg. <sup>(19,20)</sup> Raheem, et al. found that the median time to achieve target blood pressure was again faster with nifedipine compared to labetalol, 30 min. (IQR 22.5-67.5 min.) vs. 45 min. (IQR 30-60 min.); however, this difference was not statistically significant ( $p = 0.59$ ). Shekhar, et al. also found significantly faster median time to achieve targeted blood pressure with nifedipine compared to labetalol, 40 min. (IQR 20-60 min.) and 60 min. (IQR 40-85 min.), respectively ( $p = 0.008$ ). In terms of overall medication effectiveness, both studies found equivalency between oral nifedipine and intravenous labetalol. Oral nifedipine and intravenous labetalol regimens were similarly effective in acute blood pressure control. Shekhar showed a lower required median number of doses to blood pressure control (2 vs. 3;  $p = 0.008$ ) and no serious adverse maternal or perinatal drug effects were witnessed in either group. While these studies included only pregnant subjects and not the postpartum population of interest, it shows consistency with the results of the earlier Vermillion study.

In 2009, Scardo, et al. used a thoracic electrical bioimpedance technique to evaluate hemodynamic effects oral nifedipine versus intravenous labetalol in preeclamptic hypertensive emergencies in a small double blind randomized trial. Results showed a 43% increase in cardiac index ( $p = 0.0008$ ) and significant decrease in systemic vascular resistance ( $p = 0.002$ ) after nifedipine administration, while labetalol group had no such effects ( $p = 0.697$ ,  $p = 0.479$ ). Both groups showed equivalent decrease in mean arterial pressure. They hypothesize that, since Belfort, et al. had shown that preeclampsia was a fixed tissue oxygen extraction state similar to sepsis, then the increase in cardiac output caused by nifedipine may be beneficial in minimizing end organ damage. <sup>(21)</sup> Severe preeclampsia appears to be fixed tissue oxygen extraction state. Oxygen consumption is dependent on oxygen delivery. Enhanced oxygen delivery (as with enhanced cardiac index) is beneficial in critically ill non-pregnant patients. <sup>(22)</sup> Of note, this study population only included antepartum women and was a small size of only 12 total patients, all of whom received intravenous Mg-S for seizure prophylaxis.

A recent prospective observational trial in India compared the efficacy and safety of oral nifedipine and oral labetalol in treatment of hypertension related to preeclampsia. <sup>(23)</sup> Patients received either labetalol 100 mg BID or nifedipine 10 mg TID and the dose was increased every 1-2 days if required. Efficacy was measured as the number of days of oral pharmacologic therapy necessary to normalize blood pressure readings. Time to normalize blood pressure was faster with oral labetalol, 5 days (5  $\pm$  2.63 days) vs. 7.5 days with nifedipine (7.5  $\pm$  3.83 days) with  $p = 0.0015$ . Common side effects of both drugs are pedal edema (50%, 47.36%), HA (44.7%, 26.31%), and orthostatic hypotension (9%, 7%). Although the results of this study show superior efficacy of oral labetalol, there were numerous methodological problems with this study, starting with its nonrandom, non-blinded design. Judgment on treatment success was based on highest daily blood pressure reading, and study results are only provided in the form of time to normalization and not specific blood pressure measurements. Thus, these findings must be interpreted cautiously.

Two major systematic reviews have evaluated antihypertensive agents for treatment of severe pregnancy or postpartum hypertension. Firoz, et al. in 2015 reviewed 15 randomized controlled trials in pregnancy ( $n = 915$  women) and one postpartum trial. <sup>(24)</sup> The majority of studies compared oral or sublingual nifedipine (8-10 mg) to alternative agents. Nifedipine achieved treatment success in most women, similar to hydralazine (84% vs. 79%; RR 1.07 95% CI: 0.98 - 1.17) or labetalol (RR 1.02, 95% CI: 0.95 - 1.09). Target BP was achieved ~50% of time with oral labetalol (100 mg) or methyldopa (250 mg) (47% labetalol vs. 56% methyldopa; RR 0.85 95% CI: 0.54 - 1.33). Hypotension occurred in less than 2% of women. Firoz, et al. conclude that 10 mg nifedipine has the most evidence as oral antihypertensive treatment for severe hypertension in pregnancy or postpartum. Alternatively, labetalol (100 mg) and methyldopa (250 mg) are reasonable second-line options based on far more-limited data. Limitations of this review were that the majority of patients were antepartum and not postpartum. Despite a meaningful body of RCTs for nifedipine versus alternative antihypertensives, the small individual study sizes limited inter-study comparison.

Another systematic review and meta-analysis, Shekhar specifically examined the evidence for oral nifedipine compared to intravenous labetalol for safe, efficacious treatment of severe hypertension in pregnancy. <sup>(15)</sup> The pooled analysis of 7 trials, 4 from developing countries, ( $n = 363$  women-infant pairs), showed oral nifedipine associated with less risk of persistent hypertension (RR 0.42, 95% CI: 0.18 - 0.96) and maternal SEs (RR 0.57, 95% CI: 0.35 - 0.94). Oral nifedipine was associated with significantly reduced risk of persistent hypertension, reported maternal effects and neonatal death rate as compared with IV labetalol. Although difference in outcomes did not reach statistical significance, nifedipine consistently demonstrated favorable trend in multiple measures. The limitations of the study were the small number of included trials, with each having a relatively small number of participants.

There are no standardized care guidelines for management of mild to moderate postpartum hypertension, although in February 2015, ACOG published a committee opinion which included order sets for nifedipine, labetalol, and hydralazine, without recommendation on using one agent over another for management of severe hypertension. <sup>(22)</sup> The recommendation is for physicians to use personal judgment and experience to guide treatment. Thus, there is a need for a standardized guideline for timely and appropriate interventions for management of severe blood pressure during pregnancy and postpartum period. There is evidence that standardization of care can improve overall outcomes for patients. <sup>(25)</sup> Clinical care guidelines for management of patients with preeclampsia and eclampsia have been demonstrated to reduce the incidence of adverse maternal outcomes. <sup>(26)</sup>

### **Critical Points of Evidence**

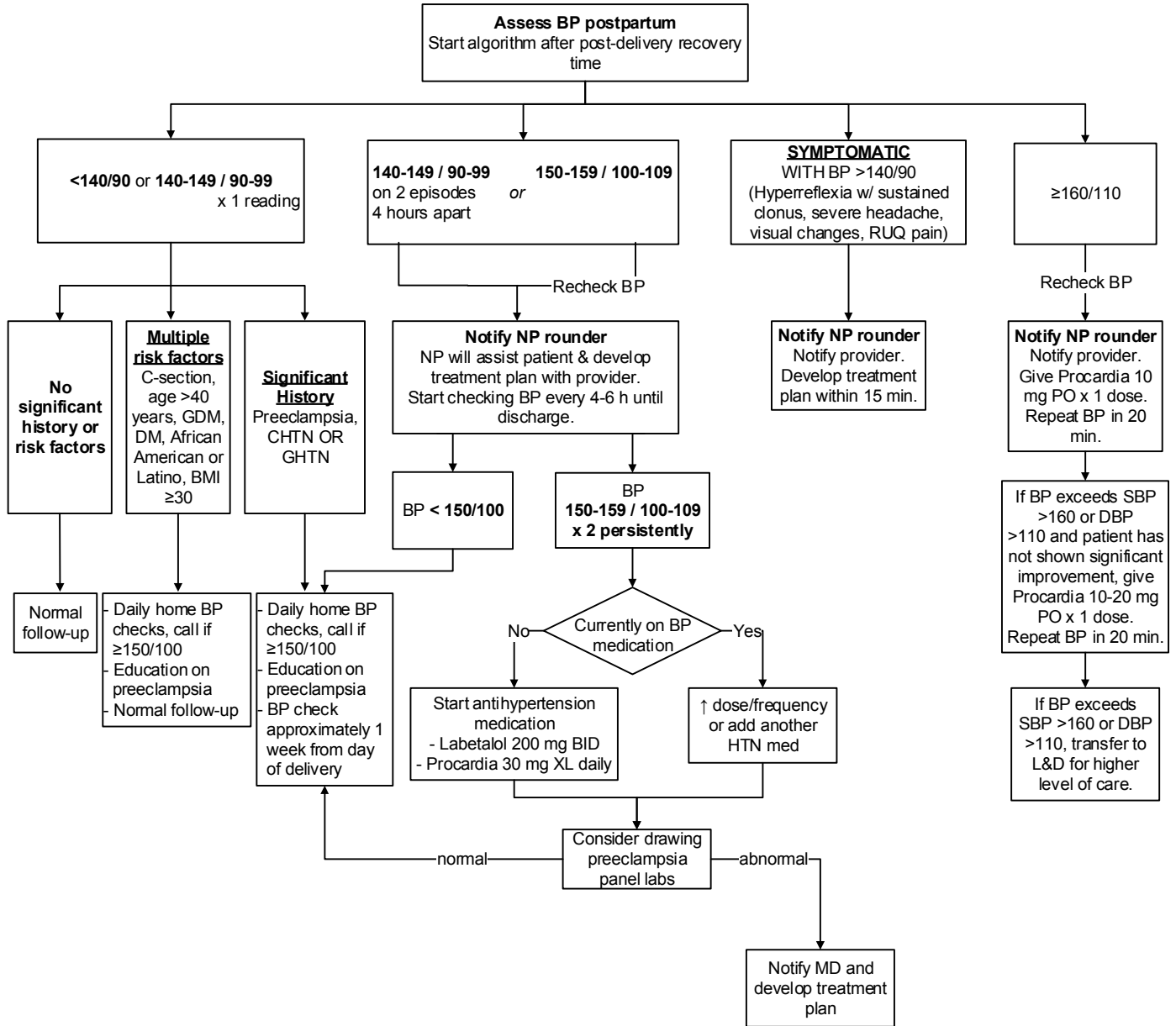
#### ***Evidence Supports***

- There is a small amount of evidence to show that patients at risk for developing de novo LPP may be identified using clinical risk factors.
- Efficacy and safety of oral nifedipine as a first line treatment for acute hypertension of pregnancy and postpartum period.
- Superiority of oral nifedipine compared to intravenous labetalol in treatment of acute hypertension of pregnancy/postpartum. Although evidence shows equivalent efficacy, several studies show faster blood pressure control and favorable secondary effects, such as increased cardiac index and increased urinary output. The side effect profile is relatively low, with <2% incidence of hypotension and no clinical evidence of cardiac depression. Nifedipine causes a slight increase in resting heart rate that does not appear to be clinically significant in most cases. There is no risk of bronchospasm and bradycardia associated with nifedipine. Finally, the easy dosing and oral route of administration of nifedipine make this a superior choice in the postpartum setting.
- Safety of oral nifedipine for treatment of acute hypertension of pregnancy and postpartum period.

#### ***Evidence Lacking/Inconclusive***

- No data to suggest that patient education and anticipatory guidance on women identified to be at risk for de novo LPP would decrease hospital readmissions or improve morbidity and mortality.
- No data to suggest that early pharmacologic intervention in the form of antihypertensive or calcium channel blockers on women identified to be at risk for de novo LPP would decrease hospital readmissions or improve morbidity and mortality.
- No data to suggest that sooner follow up times on women identified to be at risk for de novo LPP would decrease hospital readmissions or improve morbidity and mortality

**TCH Evidence-Based Outcomes Center  
Clinical Algorithm for Postpartum Elevated Blood Pressure**



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### Clinical Standards Preparation

This clinical standard was prepared by the Evidence-Based Outcomes Center (EBOC) team in collaboration with content experts at Texas Children's Hospital. Development of this clinical standard supports the TCH Quality and Patient Safety Program initiative to promote clinical standards and outcomes that build a culture of quality and safety within the organization.

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No relevant financial or intellectual conflicts to report.

### Development Process

This clinical standard was developed using the process outlined in the EBOC Manual. The literature appraisal documents the following steps:

1. Review Preparation
  - PICO questions established
  - Evidence search confirmed with content experts
2. Review of Existing Internal and External Guidelines
  - Order Set for Severe Intrapartum or Postpartum Hypertension Initial First-Line Management with Oral Nifedipine, ACOG
  - Order Set for Severe Intrapartum or Postpartum Hypertension Initial First-Line Management with Labetalol, ACOG
  - HCA Women's and Children's Clinical Services Recommend Blood Pressure Management of Severe Intrapartum or Postpartum Hypertension using Labetalol, Clark, SL
3. Literature Review of Relevant Evidence
  - Searched: PubMed, Cochrane Collaboration Database, National Guideline Clearinghouse, Clinical Trials
4. Critically Analyze the Evidence
  - 2 systematic reviews, 1 meta-analyses, 4 randomized controlled trials, and 4 nonrandomized studies
5. Summarize the Evidence
  - Materials used in the development of the guideline, evidence summary, and order sets are maintained in a Managing Postpartum Hypertension evidence-based review manual within EBOC.

### Evaluating the Quality of the Evidence

Published clinical guidelines were evaluated for this review using the **AGREE II** criteria. The summary of these guidelines are included in the literature appraisal. AGREE II criteria evaluate Guideline Scope and Purpose, Stakeholder Involvement, Rigor of Development, Clarity and Presentation, Applicability, and Editorial Independence using a 4-point Likert scale. The higher the score, the more comprehensive the guideline.

This clinical standard specifically summarizes the evidence *in support of* or *against* specific interventions and identifies where

evidence is *lacking/inconclusive*. The following categories describe how research findings provide support for treatment interventions. **"Evidence Supports"** provides evidence to support an intervention

**"Evidence Against"** provides evidence against an intervention.

**"Evidence Lacking/Inconclusive"** indicates there is insufficient evidence to support or refute an intervention and no conclusion can be drawn *from the evidence*.

The **GRADE** criteria were utilized to evaluate the body of evidence used to make practice recommendations. The table below defines how the quality of the evidence is rated and how a strong versus weak recommendation is established. The literature appraisal reflects the critical points of evidence.

Recommendation	
<b>STRONG</b>	Desirable effects clearly outweigh undesirable effects or vice versa
<b>WEAK</b>	Desirable effects closely balanced with undesirable effects
Quality	Type of Evidence
<b>High</b>	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies
<b>Moderate</b>	Evidence from RCTs with important limitations (e.g., inconsistent results, methodological flaws, indirect evidence, or imprecise results) or unusually strong evidence from unbiased observational studies
<b>Low</b>	Evidence for at least 1 critical outcome from observational studies, RCTs with serious flaws or indirect evidence
<b>Very Low</b>	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence

### Recommendations

Practice recommendations were directed by the existing evidence and consensus amongst the content experts. Patient and family preferences were included when possible. The Content Expert Team and EBOC team remain aware of the controversies in the diagnosis/management of Postpartum Hypertension. When evidence is lacking, options in care are provided in the clinical standard and the accompanying order sets (if applicable).

### Approval Process

Clinical standards are reviewed and approved by hospital committees as deemed appropriate for its intended use. Clinical standards are reviewed as necessary within EBOC at Texas Children's Hospital. Content Expert Teams are involved with every review and update.

### Disclaimer

Practice recommendations are based upon the evidence available at the time the clinical standard was developed. Clinical standards (guidelines, summaries, or pathways) do not set out the standard of care and are not intended to be used to dictate a course of care. Each physician/practitioner must use his or her independent judgment in the management of any specific patient and is responsible, in consultation with the patient and/or the patient's family, to make the ultimate judgment regarding care.

### Version History

Date	Action	Comments
Mar 2012	Originally completed	