**WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care**

**Worksheet author(s)**

| D.D. McMillan | Date Submitted for review: February 22, 2010 |

**Clinical question.**

In the neonate (preterm and term) receiving respiratory support (P), does the use of CPAP (I) versus no-CPAP or IPPV (C) improve outcome – specify (O)”

**Is this question addressing an intervention/therapy, prognosis or diagnosis?** Yes

**State if this is a proposed new topic or revision of existing worksheet:** No

**Conflict of interest specific to this question**

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? No

**Search strategy (including electronic databases searched).**

PubMed


Limits: Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Newborn: birth-1 month (13 articles – 3 selected)


Repeat Search 1 (October 2009): (3 additional articles - 1 selected).


Search 2 (February 2009): "Continuous Positive Airway Pressure"[Mesh] Limits: Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Newborn: birth-1 month (50 articles- 2 additional selected)


Repeat Search 2 (October 2009): (4 additional articles – 0 selected).

PubMed – Search 3 (February 2009)
"birth" OR "delivery" AND "pressure" AND "onset of breathing" OR "onset of respiration" – 85 articles, none selected "reflex of head" OR "heads paradoxical reflex" AND "birth" (74 articles, 1 selected)


Secondary articles – 2


Embase

Search 1 (February 2009): ('continuous positive airway pressure'/exp OR 'continuous positive airway pressure') OR ('cpap'/exp OR 'cpap') OR 'continuous distending pressure' AND [humans]/lim AND resuscitation AND [humans]/lim AND [humans]/lim AND [1976-2009]/py AND trial* OR ('research'/exp OR 'research') OR ('study'/exp OR 'study') AND [humans]/lim AND [1976-2009]/py AND ('baby'/exp OR 'baby') OR ('newborn'/exp OR 'newborn') OR neonat* AND [humans]/lim AND [1976-2009]/py (748 articles – 0 selected)

Repeat Search 1 (October 2009): (4 additional articles – 0 selected).

Search 2 (February 2009): ('birth'/exp OR 'birth') OR ('delivery room'/exp OR 'delivery room') OR 'caseroom' OR 'birth unit' AND [1976-2009]/py AND ('continuous positive airway pressure'/exp OR 'continuous positive airway pressure') OR ('cpap'/exp OR 'cpap') OR 'continuous distending pressure' AND [1976-2009]/py AND trial OR ('research'/exp OR 'research') AND [1976-2009]/py (47 articles – 0 selected).

Searches 1 & 2: (3 additional selected)


Repeat Search 2: (5 articles – 0 selected)
Cochrane Library

Keyword – continuous positive airway pressure (29 reviews, 1 selected)


Keyword – “continuous positive airway pressure” OR “CPAP” (73 articles - 3 selected)


Further Secondary Articles – 5


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<th><strong>State inclusion and exclusion criteria</strong></th>
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<tr>
<td><strong>Inclusion:</strong> CPAP within 60 minutes after birth (if not stated that CPAP was in the delivery room consider level of evidence to be 5). Includes CPAP with and without prior lung recruitment. See search strategies (include Cochrane Reviews initially to check for other studies)</td>
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| **Exclusion:** 1. Short (<5 seconds) inspiratory pressures (Inspiratory time is a topic of another worksheet)  
2. CPAP only in babies in NICU stated or presumed more than one hour after birth. |
| **Notes:** 1. Study analysis considered primary outcome (stated or presumed). Secondary outcomes were considered when they were considered to be clinically important (positive or negative) or if significant intervention was avoided by study design with neutral primary outcome.  
2. Rojas (2009) was a Level 1 design but classified as a Level 4 study as it used a treatment regimen as an alternative to CPAP which was not quite as stated in the question. |

**Number of articles/sources meeting criteria for further review:**

20 - See Search Strategy above
# Summary of evidence

## Evidence Supporting Clinical Question

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### Level of evidence

- **A** = Death or BPD
- **B** = BPD
- **C** = Need for mechanical ventilation
- **D** = Duration of mechanical ventilation
- **Italics** = Animal studies
- **With lung recruitment**

#* *= in more than one Level of Evidence
### Evidence Neutral to Clinical question

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**Level of evidence**

- **A** = Death or BPD
- **B** = BPD
- **C** = Need for mechanical ventilation
- *Italics = Animal studies*
- **D** = Duration of mechanical ventilation
- **#** = In more than one Level of Evidence
- **#* With lung recruitment**

### Evidence Opposing Clinical Question

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**Level of evidence**

- **E** = Pneumothorax
- **#** = In more than one Level of Evidence
## REVIEWER’S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

**Can brief (10-30 seconds) positive inspiratory pressure be used to assist respiration after birth?**

Brief inspiratory pressure may stimulate expiratory effort or inspiratory effort (paradoxical reflex of Head) but this has not been shown to occur in a reliable manner in asphyxiated babies. In the study by te Pas (Pediatrics 2007), a 10 second inflation (20 cm H₂O pressure) via a nasopharyngeal tube (with the mouth and nares held closed) followed by nasal CPAP in babies whose breathing was deemed insufficient in the delivery room was effective in initiating breathing in 60% of babies after one inflation and a further 15% of babies after a second inflation. It is unclear how many of these babies were apneic or if the effect might have been similar with more conventional continuous positive pressures (4-6 cm H₂O) applied for a longer period of time. Similar studies by Lindner (Acta Pediatr 2005) in babies 25-28 weeks gestation using pressures sequentially of 20, 25, and 30 cm H₂O for 15 seconds (Followed by CPAP) only reduced the need for intubation to 61% from 70% in the conventionally treated group. A subsequent report from the same centre (Linder, Pediatrics 1999) of babies <1000 g birth weight indicated the rate of intubation in the delivery room decreased from 84% to 40% with inspiratory “sighs” followed by CPAP in a retrospective cohort study. This may be beneficial but not reliable in the newborn requiring respiratory assistance for apnea.

**Is early CPAP for very preterm infants beneficial compared to oxygen alone?**

Finer (Pediatrics 2004) has demonstrated feasibility of a study with delivery room CPAP in babies <28 weeks gestation but the trial was not powered for outcomes. Sandri (Arch Dis Child, 2004) showed no benefit of early CPAP compared to waiting for CPAP until FiO₂ was >0.4 in 28-31 week gestation babies (uncertain if in delivery room) as did Han (Early Human Dev 1987) with CPAP initiated shortly after admission to NICU.

**Is early CPAP better for very preterm babies than routine intubation with administration of surfactant?**

Historical reviews of outcome after practice change with provision of CPAP suggest that early CPAP may be associated with reduced respiratory support and possibly a reduction in death or chronic lung disease although results vary from centre to centre. The study by Zecca (J Matern Fetal Neonatal Med 2006) suggests that this benefit may be in babies 27-28 weeks gestation but not more immature babies. Babies who are not intubated in the delivery room may have a lower NICU admission pH and higher pCO₂ (Lindner, Pediatrics 1999) even after lung inflation endeavors. The multicentre randomized controlled trial of early nasal CPAP versus routine intubation for ventilation and surfactant reported by Morley (NEJM 2008) is the only trial upon which to base evaluation of outcome. Differences in death and oxygen as well as death, oxygen or respiratory support were most significant at 27-28 weeks gestation with a positive trend only in the 25-26 week gestation babies. Of note, the early CPAP group had less surfactant and more pneumothoraces (possibly related) but also less intubation and assisted ventilation (by study design). Rojas (Pediatrics 2009)( reported that intubation – very early surfactant – extubation to CPAP was associated with less subsequent mechanical ventilation and less pulmonary air leak than nasal CPAP alone. No follow-up information is available to determine the effects of pneumothoraces or the primary intervention itself.

### Acknowledgements:
Citation List


Comment: This is a single centre retrospective study of 234 VLBW babies after introduction of routine 5 cm H₂O CPAP by face mask in the delivery room. Babies with apnea in delivery room were given bag and mask PPV. No response in 30 seconds led to intubation (surfactant individualized). Of 151 babies receiving delivery room CPAP, 34 were intubated within 2 days. Of 83 babies intubated in the delivery room, 28 were on CPAP by 2 days of age. Babies intubated in delivery room were smaller, more immature, more likely black and had lower Apgar scores. On multivariate analysis, later intubated early CPAP babies were more likely than initially ventilated babies to develop necrotizing enterocolitis and had a trend (p=0.06) towards decreased mortality. Comparison of babies who had early nasal CPAP with babies extubated to CPAP by two days after birth demonstrated the former had less duration of oxygen use (but were likely not as ill). Differences in patient characteristics make clinical implications uncertain.

Level of Evidence: 4
Quality: Poor
Evidence: Neutral


Comment: This is a single centre retrospective study of 261 babies <1250 g categorized as A-nasal CPAP at delivery for at least 72 hours (90); B-nasal CPAP at delivery requiring intubation when >2 hours (28); and C-babies intubated and on assisted ventilation in the delivery room (31). Success on CPAP (no assisted ventilation) favoured more mature babies (no failures after 29 weeks). Intubated babies were more likely to have RDS and symptomatic PDA. Although there was more death/BPD in babies who were initially intubated (compared to early CPAP with or without later intubation), these babies were different in terms of gestation age, Apgar scores and initial blood gases. This study was designed to look at factors associated with failure of delivery room CPAP rather than the benefits and risks of the procedure.

Level of Evidence: 2
Quality: Poor
Evidence: Neutral


Comment: In this multicentre randomized controlled feasibility trial, babies <28 weeks gestation were randomized to 5 cm H₂O face mask CPAP with 100% oxygen via T-piece or 100% oxygen without CPAP in delivery room. Pulse oximeters were used but specific guidelines for oxygenation are not indicated. There was no routine intubation for delivery room surfactant. If delivery room intubation the CPAP group only had PEEP. In NICU, both groups were placed on 5-6 cm H₂O CPAP unless stable in room air. Criteria for
intubation and surfactant were FiO$_2$ >0.3 for SpO$_2$ >90% or PaO$_2$ >45 mmHg or PaCO$_2$ >55-60 with pH <7.25 or apnea requiring bag and mask ventilation. This feasibility trial had pre-specified criteria had expected >90% compliance with specified criteria in enrolled babies (achieved compliance 91%). In CPAP group, babies were given PPV in delivery room 73% (vs 82%) and intubation in delivery room 49% (vs 41%). The percent of babies intubated in delivery room was 100% at 23 weeks, ≈5 0% at 24-26 weeks and 15% at 27 weeks. This information demonstrates very well feasibility which is primarily useful to guide future trials.

Level of Evidence: 1
Quality: Fair
Evidence: Neutral


Comment: Selected historical review of babies <1500 g in one centre before early CPAP when most babies were intubated for surfactant and time after CPAP excluded major malformation, no delivery room resuscitation and “early transfer”. Supplemental O$_2$ >2 hours or mechanical support in 44/57 babies in 1990 vs 55/70 in 1993. Frequency of intubation lower in later period (30% vs 53%). Specific criteria for support not indicated but no difference in pCO$_2$ max >60 or 65 mmHg. On logistic regression analysis early CPAP babies had higher survival (p=0.038). Intervention was indicated as “usually within 15 minutes after birth” but no specific criteria for this or assisted ventilation provided.

Level of Evidence: 3
Quality: Fair
Evidence: Supporting


Comment: This randomized controlled trial included babies <32 weeks gestation who were initially resuscitated by bag and mask ventilation. If no response in 30 sec, intubated for PPV (if improved could be extubated and included in trial). Randomization stratified by sex to early nasal pharyngeal CPAP (6 cm H$_2$O initially and then optimal CPAP determined using a fluid filled esophageal catheter) or O$_2$ by head hood. The latter babies could get CPAP if PaO$_2$ <50 mmHg in FiO$_2$ >0.5 or apnea. Nasotracheal optimal CPAP was used in both groups if PaO$_2$ <50 mmHg or further apnea in FiO$_2$ >0.8. Intubation for PPV occurred if PaO$_2$ <50 mmHg in FiO$_2$ >0.9 or pH <7.20 mainly due to pCO$_2$ or further apnea. Five of 87 babies were later excluded with anomalies or failure to follow protocol (Analysis not by intention to treat). There was no use of antenatal steroids for any baby in study. There was no difference in outcomes in 43 early CPAP and 39 control babies in terms of mortality or major morbidity (or in RDS subgroup). Communication with the author indicates babies did not receive CPAP in the delivery room ; this was initiated shortly after admission to NICU. This study lacks the power to demonstrate significant differences but may be useful in a meta-analysis.

Level of Evidence: 5
Quality: Fair
Evidence: Neutral

**Comment:** This retrospective historical study of babies ≤ 1000g and ≤ 26 6/7 weeks gestation compared periods of usual delivery room intubation with IPPV and PEEP to early variable flow CPAP. Intubation criteria were severe respiratory distress, or pCO₂ > 65mmHg and pH <7.25 or FiO₂ >0.60 (No criteria for caffeine until latter period when indications were “significant apnea” and pre-extubation). Early CPAP reduced delivery room intubation from 95% to 76%, surfactant use from 89% to 73% and later respiratory support (p 0.002). There was no change in death or chronic lung disease (multivariate analysis p=0.09 in favor of early CPAP).

Level of Evidence: 3  
Quality: Good  
Evidence: Supporting


**Comment:** This report in 2004 of the 1994-1995 Danish National study after introduction for babies <28 weeks or <1000 g of nasal CPAP “prophylactically or as early as possible” (87% from Day 1) at 3-6 cm H₂O initially and to 10 cm H₂O if needed. This included 407 babies in 16 NICUs with 269 surviving. Surfactant was given in a/A ratio <0.22. Population outcomes are described with no comparison to determine any significance of delivery room use of CPAP.

Level of Evidence: 4  
Quality: Poor  
Evidence: Neutral


**Comment:** Babies 401-1500g in one centre with introduction of use of CPAP “immediately after birth” were compared with Vermont Oxford Network data with management by routine intubation or supplemental oxygen only not specified. From 1998 to 2001, centre mortality decreased from 28% to 14% (VONN 31% to 39%). Chronic lung disease remained constant while VONN increased. Centre ROP Stage III & IV was 2% vs VONN 11%. No difference was seen in NEC or IVH. Comparison of a single centre to a network does not consider the many variable aspects of care other than delivery room CPAP making clinical significance difficult to determine.

Level of Evidence: 2  
Quality: Poor  
Evidence: Supporting


**Comment:** 61 of 95 babies 25-286/7 weeks gestations in one center were randomized using numbered opaque envelopes to 15 second nasopharyngeal tube pressure controlled lung inflation (20-25-30 cm H₂O) up to 3 times followed by 4-6 cm H₂O CPAP or IMV 20/4 – 6 cm H₂O, at 60/min unless spontaneous breathing
without support (4), major anomalies (3), feto-fetal transfusion syndrome (8), oligohydramnios before 20 weeks (4) or no consent (15). If no significant respiratory distress HR >100 bpm and SpO₂ >80 at FiO₂ <0.60 in 30 seconds, both groups had CPAP. If cyanosis, HR SpO₂ 60-80 or needed FiO₂ >0.60, HR 80-100 bpm or significant respiratory distress repeat of second inflation or another 2 minutes ventilation. The third intervention was based on same criteria. Intubation occurred if apnea at any time or HR <100 bpm or FiO₂ >0.60 to achieve preductal SpO₂ >80% after second intervention. There was a need for intubation for 61% in pressure inflation group and 70% in the IMV group. There was no difference in mortality or morbidity such as BPD. The study was not finished (calculated sample size 100) as planned as enrolment slower than expected but no significant differences in any outcome.

Level of Evidence: 1
Quality: Fair
Evidence: Neutral


Comment: This retrospective cohort study before (56) and after (67) babies <1000 g, ≥24 weeks gestation routinely had nasal pharyngeal 20 cm H₂O inflating pressure for 15-20 (mouth and other nostril held shut) seconds followed by CPAP 4-6 cm H₂O. The procedure was repeated with 25 cm H₂O inflating pressure if HR <100/minute or the baby remained cyanotic. If the baby remained with HR <100/minute, SpO₂ remained <0.80, was apneic or had marked respiratory distress, nasal PPV was provided with a mechanical ventilator. Need for delivery room intubation for PPV decreased from 84% to 40% and rate of babies never intubated increased from 7% to 25%. Antenatal Betamethasone dose increased from 8 mg to 12 mg and there was increased use in the latter period. There was no difference in mortality. Incidence of BPD, IVH > grade II and length of hospital stay significantly decreased primarily in babies who did not require intubation. There was less use of HFOV in the latter period. Babies who were not intubated in the delivery room had lower NICU admission pH and higher PCO₂. Did tolerance for lower pH and higher PaCO₂ change during this time also occur during the latter period?

Level of Evidence: 3
Quality: Good
Evidence: Supporting


Comment: This multicentre, international, randomized, controlled trial included 610 babies 25-28 weeks gestation randomly assigned to nasal CPAP or intubation and ventilation within 5 minutes after birth if ongoing respiratory support deemed necessary. Nasal CPAP started at 8 cm H₂O with intubation for apnea unresponsive to methylxanthine (6 episodes in 6 hours or >1 episode PPV) or arterial pH <7.25 with PaCO₂ >60 mmHg, metabolic acidosis unresponsive to treatment (degree and treatment unspecified) or FiO₂ >0.60. Surfactant, ventilatory management, extubation and other care were as per local care. The local pre-calculated sample size to reduce death or BPD from 30% to 20% was 600. There was no difference in mortality. Differences in death and O₂ and death, O₂ or respiratory support were only at 28 days (in babies 27-28 weeks gestation) and not at 36 weeks gestation. Fewer babies in the nasal CPAP group were intubated to receive assisted ventilation. The CPAP group had less surfactant, more methylxanthines and more pneumothoraces (9.1% vs 3.0%). Was this related to less use of surfactant? Longer term follow-up is needed to determine the potential adverse effects of pneumothoraces (although there was no difference in periventricular leukomalacia or IVH)

Comment: Retrospective study with babies 401-1000 g before (92) when babies usually intubated for surfactant and after (79) delivery room bubble CPAP (5 cm H2O) by nasal prongs. Intubation and surfactant if FiO2 >60% (SpO2 92-96%) or pH <7.15 or pCO2 >65 mmHg. Mortality with CPAP 34% (vs 38% prior) and mortality or death (68.3% vs 78.3%) not different. However, CPAP era was associated with reduced respiratory support and use of postnatal steroids with better weight gain. The primary objection of this study was to test if CPAP was safe and improved outcomes. What else may have changed between periods?


Comment: This study compares early nasal CPAP alone with intubation for surfactant and rapid extubation to nasal CPAP. The latter was associated with less mechanical ventilation but more pulmonary air leak. Mortality and/or chronic lung disease were not significantly different. This study does not compare CPAP versus no CPAP but provides another treatment regimen which may address concerns that early CPAP alone may be associated with increased pneumothoraces.


Comment: This randomized controlled trial in 17 Italian NICUs compared nasal prong CPAP started within 30 minutes after birth to oxygen by hood in babies 28-31 weeks gestation. If on CPAP and FiO2 >0.4 to keep SpO2 93-96% babies were placed on CPAP. All babies on CPAP with FiO2 >0.4 were intubated for surfactant and extubated to CPAP. Mechanical ventilation was provided if FiO2 >0.4 after surfactant, severe apnea (>4/hour or two bag and mask interventions/hour) or pH <7.2 with pCO2 >70 mmHg. Of 423 eligible patients, 115 were assigned to early CPAP and 115 to the head box oxygen group of whom 66 later had CPAP. There was no difference in mortality or major morbidity. If CPAP is not started very shortly after birth, the study suggests waiting until need for FiO2 >0.40 is equally effective for babies 28-31 weeks gestation.

Comment: This is a single centre, case control study comparing 25/87 babies (those with RDS requiring later intubation with early nasal CPAP (4 at birth and 83 within 15 minutes of NICU arrival) with 4-8 cm H$_2$O pressure to 50 equivalent gestation control babies intubated in the delivery room and who had RDS. Methylxanthines were given after birth to all babies <30 weeks gestation and selectively to others. Criteria for surfactant (MAP x FiO2 >2 and extubation to CPAP (FiO2 <0.3 with MAP < 7 cm H$_2$O) were given. Early CPAP (but later intubation for ventilation) babies received fewer doses of surfactant (1 +/- 0.5 vs 1.6 +/- 0.8) and had less BPD. There are not specific criteria for intubation. The analysis was not by intention to treat but a selected subgroup of babies. This does not indicate whether early CPAP decreases the need for subsequent intubation or has other benefits or hazards.

Level of Evidence: 2
Quality: Poor
Evidence: Neutral


Comment: In this single centre randomized controlled trial 207 infants < 33 weeks gestation were assigned prior to birth to early functional residual capacity intervention (EFRCI) or bag and mask ventilation if breathing was insufficient. EFRCI protocol indicated after suctioning, if apnea or breathing with poor air entry – a 10 sec, 20 cm H$_2$O inflation was applied via T-piece and nasopharyngeal tube (mouth and other nares held closed). This was repeated in 1 minute using 25 cm H$_2$O if breathing was insufficient, HR <100 bpm or the baby was cyanotic (FiO2 not specified) but O2 started at 100%. If breathing sufficient 5-6 cm H$_2$O CPAP was continued. If baby was not improved and HR >100/min nasal IPPV was used. If HR <100/min, cyanosis or marked respiratory distress the baby was intubated. Control group babies had self-inflation bag and mask ventilation with an initial pressure of 30-40 cm H$_2$O and then <20 cm H$_2$O peak inspiratory pressure. All babies got methylxanthines shortly after birth. Surfactant was given to all intubated babies in the NICU. Criteria for extubation was FiO2 <0.3 and MAP <7 cm H$_2$O. 38/104 EFRCI babies and 52/103 convention babies were intubated within 72 hours of birth (p=0.04). In EFRCI group 44 of the 73 babies who received EFRCI stabilized after one inflation and 29 needed a second inflation, 18 of whom needed delivery room intubation (compared to 37/103 in conventional group). There were less overall intubations at 28-30 weeks gestation and no difference in younger and older babies. Fewer EFRCI babies received >1 dose surfactant. There was no difference in mortality but BPD was reduced in EFRCI group. The ten second lung inflation may be different than sustained CPAP. This does suggest a potential difference in response according to gestation with early CPAP possibly more effective at 28-30 weeks gestation.

Level of Evidence: 1
Quality: Good
Evidence: Supporting

**Comment:** This retrospective comparative study of two NICUs included babies <28 weeks gestation. In Stockholm there was routine nasal CPAP (specific methods not indicated). These babies had more antenatal steroids but higher SNAPPE-II scores. In Boston, babies were routinely intubated for surfactant. Excluding anomalies and early transfer, 70 Boston and 102 Stockholm babies had similar mortality although causes were different – cardiorespiratory (58% in Boston vs 27% in Stockholm), IVH grade 3 or 4 (33% vs 17%) and sepsis (8% vs 44%). In Stockholm 44% of babies were intubated in delivery room and 35% later with 22% never intubated. Odd ratio of death or moderate/severe BPD at 40 weeks of 0.40 (95% CI 0.18-0.86) favored Stockholm on multivariate anlaysis. The significance of variable outcomes at different sites is unclear as there are many other potential factors to consider.

Level of Evidence: 2  
Quality: Poor  
Evidence: Supporting


**Comment:** This is a retrospective cohort study of babies 24-28 weeks gestation with elective intubation or nasal CPAP in delivery room if spontaneous breathing (intubation later if pH <7.25 and pCO₂ >60 mmHg). All babies had caffeine, prophylactic ibuprofen and, if RDS, surfactant. Fewer babies were never intubated (3.1%) in the first period with 14.1% never intubated in the nasal CPAP period (significant in 27-28 week babies only). CPAP babies survival 70.5% vs 53.1% (p <0.02) was significant only in 27-28 week babies (79% vs 63%). Benefit in terms of less ROP surgery, less PDA and shorter length of stay occurred in 27-28 week babies only. This suggests potential benefit may be confined to babies above 26 weeks gestation.

Level of Evidence: 3  
Quality: Good  
Evidence: Supporting