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Management of Clinical Chorioamnionitis: An Evidence-Based Approach

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Abstract

The aim of this review was to examine the existing evidence about interventions proposed for the treatment of clinical chorioamnionitis, with the goal of developing an evidence-based contemporary approach for the management of this condition. Most trials that assessed the use of antibiotics in clinical chorioamnionitis included patients with a gestational age ≥34 weeks and in labor. The first-line antimicrobial regimen for the treatment of clinical chorioamnionitis is ampicillin combined with gentamicin, which should be initiated during the intrapartum period. In the event of a cesarean delivery, patients should receive clindamycin at the time of umbilical cord clamping. The administration of additional antibiotic therapy does not appear to be necessary after vaginal or cesarean delivery. However, if post-delivery antibiotics are prescribed, there is support for the administration of an additional dose. Patients should receive antipyretics, mainly

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acetaminophen, even though there is no clear evidence of their benefits. Current evidence suggests that the administration of antenatal corticosteroids for fetal lung maturation and of magnesium sulfate for fetal neuroprotection to patients with clinical chorioamnionitis between 24 0/7 and 33 6/7 weeks of gestation, and possibly between 23 0/7 and 23 6/7 weeks, has an overall beneficial effect on the infant. However, delivery should not be delayed in order to complete the full course of corticosteroids and magnesium sulfate. Once the diagnosis of clinical chorioamnionitis has been established, delivery should be considered, regardless of the gestational age. Vaginal delivery is the safer option and cesarean delivery should be reserved for standard obstetric indications. The time interval between the diagnosis of clinical chorioamnionitis and delivery is not related to most adverse maternal and neonatal outcomes. Patients may require a higher dose of oxytocin to achieve adequate uterine activity and/or greater uterine activity to effect a given change in cervical dilation. The benefit of using continuous electronic fetal heart rate monitoring in these patients is unclear. We identified the following promising interventions for the management of clinical chorioamnionitis: (1) an antibiotic regimen including ceftriaxone, clarithromycin, and metronidazole that provides coverage against the most commonly identified microorganisms in patients with clinical chorioamnionitis; (2) vaginal cleansing with antiseptic solutions before cesarean delivery with the aim of decreasing the risk of endometritis and, possibly, postoperative wound infection; and (3) antenatal administration of N-acetylcysteine, an antioxidant and anti-inflammatory agent, to reduce neonatal morbidity and mortality. Well-powered randomized controlled trials are needed to assess these interventions in patients with clinical chorioamnionitis.

Keywords

abnormal fetal heart rate patterns; abnormal labor progression; adverse maternal outcomes; adverse neonatal outcomes; antenatal corticosteroids; antibiotics; antipyretics; cerebral palsy; cesarean delivery; continuous electronic fetal heart rate monitoring; fever; intra-amniotic infection; intra-amniotic inflammation; magnesium sulfate; management of labor; maternal infection; N-acetylcysteine; neonatal sepsis; neuroprotection; postpartum hemorrhage; prolonged labor; vaginal cleansing

INTRODUCTION

Clinical chorioamnionitis is the most common infection-related complication in labor and delivery units worldwide, affecting 1–6% of pregnancies in the United States.[1–7] This syndrome is a well-known risk factor for adverse maternal outcomes such as postpartum hemorrhage secondary to uterine atony,[8,9] uterine rupture,[5] unplanned hysterectomy,[7] blood transfusion,[5–8] postoperative wound infection,[6,10] endometritis,[6,11] pelvic abscess,[8] septic pelvic thrombophlebitis,[8,12] sepsis,[13–15] and intensive care unit admission,[5–7] among others.

Neonates born to mothers diagnosed with clinical chorioamnionitis are at higher risk for low Apgar scores at 5 minutes,[7,8,16] neonatal seizures,[7,8,16,17] neonatal sepsis,[8,16–22] bronchopulmonary dysplasia,[23,24] intraventricular hemorrhage (IVH),[18,25,26] periventricular leukomalacia,[24,26–28] use of mechanical ventilation,[7,17] admission to the neonatal intensive care unit (NICU),[17] neonatal death,[2,7,20] and long-term infectious morbidity[29] compared to neonates born to women without this syndrome. Evidence regarding the association between clinical chorioamnionitis and the risk of cerebral palsy and long-term adverse

neurodevelopmental outcomes is conflicting: some studies reported a positive association, [20,30–35] whereas others did not.[36–40]

Clinical chorioamnionitis has been traditionally diagnosed by the presence of maternal fever (temperature ≥37.8°C or ≥38.0°C) plus two or more of the five following clinical signs: maternal tachycardia (heart rate >100 beats/min), fetal tachycardia (heart rate >160 beats/min), uterine tenderness, purulent or foul-smelling amniotic fluid or vaginal discharge, and maternal leukocytosis (white blood cell count >15,000/mm^3).[41–43] The diagnostic accuracy of these criteria to identify patients with proven intra-amniotic infection is about 50%.[44]

Fifteen percent of cases of clinical chorioamnionitis are diagnosed in the antepartum period and 85% in the intrapartum period.[6] The most frequent microorganisms identified in the amniotic fluid of women with clinical chorioamnionitis include *Ureaplasma urealyticum*, *Gardnerella vaginalis*, *Mycoplasma hominis*, *Streptococcus agalactiae*, *Lactobacillus* species, and *Bacteroide*s species.[45–59] Polymicrobial invasion of the amniotic cavity is present in approximately 50% of cases.[45,46,51,52]

Ascending microbial invasion from the lower genital tract appears to be the most frequent pathway for intra-amniotic infection.[49,52,60–62] However, hematogenous dissemination of microorganisms from the oral cavity or intestine, retrograde seeding from the peritoneal cavity through the fallopian tubes, and accidental introduction at the time of an invasive medical procedure have also been proposed as potential pathways for intra-amniotic infection.[49,52,62–69]

Clinical chorioamnionitis is typically thought to occur as a result of microbial invasion of the amniotic cavity, which can elicit systemic and local inflammatory responses.[49,62,70–74] However, recent studies have shown that microbial invasion of the amniotic cavity is present in only 61% of women with clinical chorioamnionitis at term[45] and in 34% of those with preterm clinical chorioamnionitis.[46] Intra-amniotic inflammation (amniotic fluid interleukin-6 concentration ≥ 2.6 ng/mL) is detected in ~77% of patients with preterm or term clinical chorioamnionitis.[45,70] Overall, 24% of patients with preterm clinical chorioamnionitis[46] and 15% of patients with clinical chorioamnionitis at term[45,70] have no evidence of either intra-amniotic infection or intra-amniotic inflammation. Recent studies in women with clinical chorioamnionitis at term have characterized the nature of the maternal and fetal inflammatory response through identification of profiles of cytokines and leukocytes in amniotic fluid,[70,72,73,75,76] maternal plasma,[77] and umbilical cord plasma.[78]

The standard treatment for clinical chorioamnionitis has been administration of antibiotics and antipyretics and expedited delivery.[79–82] However, the management of patients with this condition presents several clinical challenges. A survey conducted among US obstetricians revealed a wide variation in practice patterns for the management of clinical chorioamnionitis, including the use of more than 25 different primary antibiotic regimens and postpartum antibiotic duration ranging from no treatment to 48 hours of postpartum treatment.[83] Therefore, a rigorous, up-to-date evaluation of the interventions proposed for the management of clinical chorioamnionitis is necessary. The objectives of this review were (1) to examine and summarize the existing evidence regarding interventions proposed for

treating clinical chorioamnionitis; (2) to develop an evidence-based approach for the contemporary management of this condition; and (3) to identify promising interventions in this field.

In 2015, an expert panel proposed to replace the term clinical chorioamnionitis with the term "intrauterine inflammation or infection or both", abbreviated as "Triple I".[84] However, this proposal has not gained popularity because it implies that the inflammatory status of the amniotic cavity and the presence of microorganisms have been established, and this is rarely the case. Therefore, we continue to use the term "clinical chorioamnionitis" to refer to this syndrome.

A literature search for articles related to the treatment of clinical chorioamnionitis was conducted in MEDLINE, EMBASE, POPLINE, LILACS, CINAHL, the Cochrane Central Register of Controlled Trials, clinical trial registries (all from their inception to June 30, 2020), and Google Scholar using the terms *chorioamnionitis*, *intra-amniotic infection*, *intra-amniotic inflammation, amniotic fluid infection*, *amnionitis*, and *intrauterine infection*. There were no language restrictions. We prioritized data from randomized controlled trials and systematic reviews and meta-analyses of randomized controlled trials. Case series, observational studies, systematic reviews and meta-analyses of observational studies, review articles, and guidelines of major professional societies were also reviewed. Selected articles were mutually agreed upon by the authors. We updated the meta-analyses if we located eligible studies that had been published after the latest literature search date.

Antibiotics

There is a broad consensus that women with a diagnosis of clinical chorioamnionitis should receive antibiotic therapy to prevent adverse maternal and perinatal outcomes.[84–98] Based on information about amniotic fluid microbiology of patients with clinical chorioamnionitis, several antibiotic regimens have been proposed. Nevertheless, most microbiological studies were performed before the introduction of molecular techniques and did not include specific cultures for genital Mycoplasmas. Therefore, the antibiotic regimens that have been assessed in randomized controlled trials pre-date the modern understanding of the microbiology of the amniotic cavity in clinical chorioamnionitis and intra-amniotic infection.[45–53,58,59,62]

We identified 14 randomized controlled trials[99–112] (Table 1) and one systematic review and meta-analysis[113] that assessed the use of antibiotics in women with clinical chorioamnionitis. Most trials included patients with a gestational age ≥34 weeks and in labor. No study reported results separately for patients with clinical chorioamnionitis before 34 weeks of gestation and/or those not in labor. Therefore, the findings of these trials might not apply to patients with these characteristics.

Timing of antibiotic therapy initiation

Evidence suggests that antibiotic administration should be initiated in the intrapartum period when the diagnosis of clinical chorioamnionitis is made. This recommendation is based on the findings of a randomized controlled trial that compared intrapartum (N=26) versus postpartum (immediately after umbilical cord clamping; N=19) treatment with antibiotics in patients with a gestational age >34 weeks and a diagnosis of "intra-amniotic infection",

which was based on clinical criteria.[99] The antimicrobial agents used were ampicillin and gentamicin. In both study groups, patients who underwent cesarean delivery also received clindamycin after cord clamping to extend coverage for anaerobic organisms.

Intrapartum antibiotic treatment was associated with a significant reduction in the frequency of neonatal pneumonia or sepsis (0.0% vs. 31.6%, $P = 0.046$) and a decrease in neonatal hospital stay (3.8 days vs. 5.7 days; $P = 0.02$), maternal postpartum hospital stay (4.0 days vs. 5.0 days, $P = 0.04$), and maternal febrile days (0.4 days vs. 1.5 days, $P = 0.03$). Similar results were reported in two nonrandomized studies that compared antibiotic administration during labor versus immediately postpartum.[114,115]

Selection of antibiotics and regimens

Thirteen trials compared two antibiotic regimens during the intrapartum (5 trials)[100–104] and intrapartum/postpartum (8 trials)[105–112] periods. Overall, there were no significant differences in maternal and neonatal infectious morbidity between the antibiotic regimens assessed in the individual trials (Table 1). Nine of these trials[101–106,109–111] used ampicillin 2 g intravenously (IV) every 6 hours combined with gentamicin 1.5–2.0 mg/kg IV every 8 hours or 4.0–5.0 mg/kg IV every 24 hours. In five trials, patients who underwent cesarean delivery also received clindamycin at the time of umbilical cord clamping (usually 900 mg IV single dose).[103,104,109–111] The second most frequently used antibiotic regimen during the intrapartum period was ampicillin/sulbactam 3 g IV every 6 hours.[100,104] A trial that compared ampicillin combined with gentamicin (N=49) versus ampicillin/sulbactam (N=43) for 24 hours after delivery reported no significant differences in the frequency of maternal postpartum infection (0.0% vs. 8.2%, $P = 0.16$) and neonatal sepsis (2.3% vs. 4.1%, $P = 0.64$) between the two antibiotic regimens.[104]

Two trials compared the combination of ampicillin and gentamicin once-daily versus ampicillin and gentamicin thrice-daily.[102,103] A meta-analysis of the two trials (N=163) showed no significant differences between the two antibiotic regimens in the risk of endometritis (relative risk [RR] 0.86, 95% confidence interval [CI] 0.27–2.70) and neonatal sepsis (RR 1.07, 95% CI 0.40–2.86),[113] which suggests that the once-daily dosing regimen of gentamicin is as effective as the thrice-daily dosing. A recent nonrandomized study reported that gentamicin once-daily significantly reduced the risk of postpartum endometritis in patients with clinical chorioamnionitis, as compared to gentamicin thrice-daily.[116]

In summary, although there is insufficient data to demonstrate the most appropriate antimicrobial regimen for the treatment of this obstetric condition, current available evidence indicates that women with clinical chorioamnionitis, mainly those with a gestational age ≥34 weeks and in labor, can be treated with ampicillin 2 g IV every 6 hours combined with gentamicin 5 mg/kg every 24 hours or 1.5 mg/kg every 8 hours, or ampicillin/sulbactam 3 g IV every 6 hours. In the event of cesarean delivery, patients should receive clindamycin 900 mg IV at the time of umbilical cord clamping. Based on expert opinion, metronidazole 500 mg IV has been proposed as an alternative to clindamycin in the event of cesarean delivery.[84,85,87,93,95,96] In penicillin-allergic patients, clindamycin 900 mg IV every 8 hours or vancomycin 1 g IV every 12 hours or erythromycin 500 mg-1 g IV every 6 hours can be used instead of ampicillin.[85,87,93,94,96] Studies assessing the use of antibiotics among

women with clinical chorioamnionitis before 34 weeks of gestation and those not in labor are needed to determine the most appropriate regimen in this subset of patients.

Ureaplasma species are the most common microorganisms isolated from the amniotic fluid of patients with clinical chorioamnionitis.[45–53,58,59,62,117–119] The antibiotics that were used in the randomized controlled trials shown in Table 1 do not provide coverage against *Ureaplasma* species and *mycoplasma* species.[120] Recently, the successful use of an antibiotic regimen, i.e., ceftriaxone 1 g IV every 24 hours, clarithromycin 500 mg orally every 12 hours, and metronidazole 500 mg IV every 8 hours, has been reported among women with preterm prelabor rupture of membranes (PROM),[121,122] and a subset of patients with confirmed intra-amniotic infection/inflammation and preterm labor with intact membranes[123] or cervical insufficiency.[124,125] The rationale for using this antibiotic regimen was as follows: clarithromycin for its much higher rate of transplacental passage than erythromycin or azithromycin and its effectiveness against *Ureaplasma* species and *mycoplasma* species; ceftriaxone for its enhanced coverage of aerobic bacteria and high rate of transplacental passage; and metronidazole for its optimal coverage of anaerobic microorganisms. We believe that this new antibiotic regimen, using clarithromycin 500 mg IV (instead of orally) every 12 hours, should be the subject of study in patients with clinical chorioamnionitis given the high concordance between microorganisms associated with clinical chorioamnionitis[44–59] and those associated with confirmed infection/inflammation and preterm PROM, preterm labor with intact membranes, and cervical insufficiency.[121–124] These studies should determine whether clarithromycin eradicates *Ureaplasma* species and *mycoplasma* species in patients with clinical chorioamnionitis in whom these microorganisms are identified, and whether this eradication is associated with an improvement in maternal and neonatal outcomes.

Alternative antibiotic regimens that have been proposed for the treatment of clinical chorioamnionitis are shown in Table 2.[10,87,91,96,97,100,126–129] None of these regimens have been tested in randomized controlled trials and most of them have been recommended based on expert opinion.

Use of antibiotics after delivery

Two trials compared the use of antibiotics versus placebo in the postpartum period after vaginal delivery.[105,108] One trial (N=38) compared ampicillin combined with gentamicin for 48 hours versus placebo,[105] and the other (N=250) compared gentamicin combined with clindamycin versus placebo (duration was not reported).[108] Both studies reported non-significant differences between the antibiotic and placebo groups in the frequency of "treatment failure", defined as a temperature >38 °C after the first postpartum antibiotic or placebo dose in one trial,[105] and persistent fever after the third dose of the study drug or readmission for endomyometritis in the other trial.[108] A meta-analysis of the two studies (N=288) showed no significant difference in the frequency of "treatment failure" between the antibiotic and placebo groups (2.0% vs 3.6%; RR 0.55, 95% CI 0.13–2.29; $P = 0.41$).

Two trials assessed the use of antibiotics versus non-use of antibiotics after cesarean delivery.[109,111] Both trials included only laboring patients with preterm or term gestations and clinical chorioamnionitis. One study (N=116) compared gentamicin combined with

clindamycin until afebrile for a minimum of 24 hours versus no antibiotics;[109] another (N=80) compared one additional postpartum dose of gentamicin and clindamycin versus no antibiotics.[111] There were no significant differences in the frequency of endometritis and wound infection between the study groups in both trials. A meta-analysis of the two trials (N=196) showed no significant differences in the risk of endometritis (16.7% vs 12.0%; RR 1.42, 95% CI 0.72–2.83; $P = 0.31$) and wound infection (8.3% vs 5.0%; RR 1.30, 95% CI 0.15–10.98; $P = 0.81$) between the antibiotic and no-antibiotic groups.

Two trials, one among patients who delivered vaginally (N=46)[112] and another among patients who delivered either vaginally or by cesarean section (N=292),[110] compared a single antibiotic dose after delivery versus continued use of antibiotics until afebrile for 24 hours. In both studies, there were no significant differences between the single antibiotic dose group and the continued use of antibiotics group in the frequency of "treatment failure", defined as a single temperature ≥39.0 °C after the first postpartum dose of antibiotics or two temperatures ≥38.4 °C at least 4 hours apart in one study,[110] and endometritis and postpartum fever in the other study.[112]

In summary, even though there is limited information to guide the appropriate use of antibiotics after delivery in patients with clinical chorioamnionitis, current evidence suggests that antibiotic administration may not be necessary after vaginal or cesarean delivery. However, if post-delivery antibiotics are prescribed, one additional dose of the antibiotic regimen appears to be as effective as continued use of antibiotics to reduce the risk of maternal infection. A longer duration of antibiotic therapy may be required in patients with persistent fever, bacteremia, or sepsis in the postpartum period.

Antipyretics

Maternal intrapartum fever has been associated with a higher frequency of fetal tachycardia,[130,131] intervention for non-reassuring electronic fetal monitoring,[132] operative vaginal delivery,[133–135] cesarean delivery,[130,133–136] neonatal depression,[130,133,135–141] neonatal encephalopathy,[137,138,140,142–144] perinatal arterial ischemic stroke,[144,145] neonatal seizures,[137,138,139,144,146–148] and NICU admission.[130,132,133,135,136] The extent to which these complications are a result of maternal fever is uncertain. It is possible that antipyretic administration to patients with intrapartum fever can reduce adverse obstetric and neonatal outcomes.

Acetaminophen has been the most recommended antipyretic in patients with clinical chorioamnionitis.[88,92,94–97] It can be administered orally, rectally, or IV. Serum peak levels (~12 μg/ml) and half-life (~1.5 hours) of acetaminophen in pregnant women are similar to those in non-pregnant adults.[149] The conventional oral dose of acetaminophen is 325–650 mg every 4–6 hours; total daily doses should not exceed 4 g. Unfortunately, studies on the effect of acetaminophen on maternal and fetal temperatures during labor, as well as on adverse obstetric and neonatal outcomes are sparse and show conflicting results. In 1989, a case series study reported on the effects of acetaminophen administration (650 mg rectally) in eight febrile patients with clinical chorioamnionitis.[150] When the temperature remained >38.3°C, the dose was repeated in one to two hours. Acetaminophen administration resulted in a mean decrease in temperature of 1.2°C. In addition, the fetal heart rate tracings at the

peak of the maternal fever, characterized by tachycardia, decreased variability and late decelerations, changed to a normal heart rate pattern without decelerations when the mother's fever was reduced. Moreover, significant improvements in acid-base status were noted at birth as compared to that of the fetal scalp blood at the peak of the maternal fever.

A nonrandomized study reported that acetaminophen administration in women with intrapartum fever was associated with a significant decrease in the frequency of failure to progress in labor in comparison to no administration of acetaminophen (16% [20/122] vs 32% [12/38], $P = 0.04$).[132] There was no evidence of an effect of acetaminophen on the presence of meconium in the amniotic fluid, intervention for non-reassuring electronic fetal monitoring, or NICU admission. In 2013, a study reported that the administration of acetaminophen 1000 mg orally to women with intrapartum fever ≥38.0°C (N=18) decreased neither maternal axillary nor fetal scalp temperatures; however, acetaminophen halted ongoing increases in fetal temperatures.[151] A reanalysis of study data demonstrated that both maternal and fetal temperatures decreased after acetaminophen administration.[152] A more recent nonrandomized study, including 54 patients with intrapartum fever ≥ 38°C of which only three had a diagnosis of clinical chorioamnionitis, reported no significant differences between patients who received acetaminophen 650 mg orally (N=41) and those who did not (N=13) in the frequency of cesarean delivery, presence of meconium, requirement for neonatal bag/mask ventilation, requirement for continuous positive pressure ventilation, and NICU admission.[130]

Intravenous acetaminophen might be useful when patients are unable to tolerate oral administration or when an earlier onset of action is desirable. Indeed, intravenous acetaminophen has increased bioavailability and more rapid onset of action.[153] Recently, it was reported that two patients with intrapartum fever and fetal tachycardia had a reduction of maternal temperature and resolution of fetal tachycardia 20 minutes after administration of acetaminophen 1 g IV.[154] A randomized controlled trial comparing intravenous acetaminophen versus oral acetaminophen in women in active labor with a fever >38.0°C is ongoing (NCT02625454).[155]

In conclusion, although there is no clear evidence that the treatment of intrapartum fever reduces the risk of adverse obstetric and neonatal outcomes, antipyretics, mainly acetaminophen, have been used to treat hyperthermia in patients with clinical chorioamnionitis. Randomized controlled trials evaluating the effects of acetaminophen on intrapartum fever and both obstetric and neonatal outcomes in women with clinical chorioamnionitis are necessary.

Antenatal corticosteroids

Currently, there is a broad consensus for administering a single course of antenatal corticosteroids (ACS) between 24 0/7 and 33 6/7 weeks of gestation to pregnant women at risk of preterm delivery within 7 days.[156–165] Some professional organizations recommend that ACS may also be considered for women between 23 0/7 and 23 6/7 weeks of gestation[156,157,159,161,162,166] and between 34 0/7 and 36 6/7 weeks of gestation[156,161,167] who are at risk of preterm delivery within 7 days.

The use of ACS among women with clinical chorioamnionitis remains controversial given the immunosuppressive effects, which, theoretically, could exacerbate systemic infections or activate latent infections in the mother, or increase the risk of neonatal infection. Some clinical guidelines advise against the use of ACS for fetal lung maturation in patients with clinical chorioamnionitis,[160,163] others advise caution in its use,[162,164] and one openly recommends its use in these patients.[158] To date, there are no published randomized controlled trials evaluating the efficacy and safety of ACS in women with clinical chorioamnionitis. Only four of 30 trials included in the Cochrane review on ACS in women at risk for preterm birth reported that they included a proportion of women (2–15%) who had a diagnosis of clinical chorioamnionitis at trial entry.[168] Nevertheless, no studies reported results for this subset of pregnant women.

Two meta-analyses of nonrandomized studies of interventions, one[169] including seven studies (1335 women)[170–176] and another[177] including eight studies (1424 women),[170–176,178] evaluated the effects of ACS administration to women with clinical or histologic chorioamnionitis before 34 weeks of gestation on adverse neonatal outcomes. Overall, ACS administration was associated with (1) significant decrease in the risk of neonatal death and other adverse neonatal outcomes among infants born to women diagnosed with histologic chorioamnionitis, and (2) significant reduction in a few adverse neonatal outcomes among neonates born to women with clinical chorioamnionitis.

We updated these meta-analyses by incorporating three nonrandomized studies that assessed the effect of ACS administration in women with histologic chorioamnionitis on neonatal outcomes[179,180] and on mortality and neurodevelopmental outcomes at 3 years of age[181] (Table 3). Compared to infants born to mothers with histologic chorioamnionitis who did not receive ACS, infants born to mothers with histologic chorioamnionitis who received any ACS (≥1 dose) had a significantly lower risk of neonatal morbidity and mortality. Importantly, ACS administration significantly decreased the risk of neonatal sepsis (odds ratio [OR] 0.76, 95% CI 0.63–0.93). Among infants born to mothers with clinical chorioamnionitis, the administration of ACS was associated with a significant reduction in the risk of any IVH and periventricular leukomalacia. There were no significant differences between the ACS and non-ACS groups in other adverse neonatal outcomes as well as in neurodevelopmental outcomes.

The most important limitation of this updated meta-analysis is the lack of information in the included studies about the timing of ACS administration relative to the diagnosis of clinical chorioamnionitis. It is noteworthy that none of the primary studies provided data on adverse maternal outcomes. However, the use of ACS in women with clinical chorioamnionitis was not associated with a significant increase in any adverse neonatal outcome, and this was also the case in retrospective studies comparing patients with and without histologic chorioamnionitis.

In a Cochrane review, ACS administration to women with preterm PROM significantly decreased the risk of neonatal death (RR 0.61, 95% CI 0.46–0.83), RDS (RR 0.70, 95% CI 0.55–0.90), and IVH (RR 0.47, 95% CI 0.28–0.79), with no evidence of an effect on the risk of chorioamnionitis (RR 0.98, 95% CI 0.69–1.40), endometritis (RR 1.02, 95% CI 0.35–

2.97), or puerperal sepsis (RR 1.11, 95% CI 0.55–2.25).[168] Given that the frequency of microbial invasion of the amniotic cavity in women with preterm PROM ranges from 20–50%,[182–189] it seems logical that ACS administration may be beneficial in patients with clinical chorioamnionitis.

Considering >90% of patients with clinical chorioamnionitis are expected to deliver within 12 hours of diagnosis,[6,8,79,99,102,114,190–193] most will receive only one dose of ACS. Nonetheless, there is evidence from observational studies showing that infants exposed to an incomplete course of ACS had a significantly lower risk of death and/or other adverse neonatal or neurodevelopmental outcomes compared to infants not exposed to ACS.[194–200] In addition, a subgroup analysis of the Cochrane review showed that ACS administration reduces the risk of neonatal death in infants who are born less than 24 hours after the first dose has been administered (RR 0.53, 95% CI 0.29–0.96).[201] Noticeably, the authors of a recent population-based prospective cohort study reported that if patients received ACS at least 3 hours before delivery, there was a 26% decrease in neonatal mortality. If they received ACS 3 to 5 hours before delivery, there was a 37% decrease in neonatal mortality, and if patients received ACS 6 to 12 hours before delivery, there was a 51% decrease in neonatal mortality.[198]

In summary, current available evidence suggests that the administration of at least one single dose of ACS to patients with clinical chorioamnionitis has an overall beneficial effect on the neonate without increasing the risk of sepsis or other adverse neonatal outcomes. Thus, it appears reasonable to administer ACS to women with clinical chorioamnionitis between 24 0/7 and 33 6/7 weeks of gestation and to consider its administration to those with a gestational age between 23 0/7 and 23 6/7 weeks. Delivery should not be delayed in order to complete the full course of ACS.

Magnesium sulfate for fetal neuroprotection

Currently, there is strong evidence from several systematic reviews and meta-analyses that magnesium sulfate administered to women at risk of imminent preterm delivery reduces the risk of cerebral palsy in their children by about 32%.[202–205] Antenatal magnesium sulfate is also associated with a significant reduction in the risk of moderate or severe cerebral palsy and substantial gross motor dysfunction. Although most clinical guidelines recommend the administration of magnesium sulfate for fetal neuroprotection to women at risk of imminent preterm delivery (expected within 2–24 hours) regardless of the reason for preterm birth, there is controversy with respect to gestational age at treatment (from “viability” or 24 0/7 weeks to 29 6/7 weeks,[206] 31 6/7 weeks[160,207] or 33 6/7 weeks[167,208]). Some guidelines recommend that magnesium sulfate administration should also be considered for women at risk of imminent delivery between 23 0/7 and 23 6/7 weeks.[157,166] An individual patient data (IPD) meta-analysis[205] of five trials[209–215] of magnesium sulfate for fetal neuroprotection reported no significant differences in the beneficial effect of this intervention on cerebral palsy among subgroups based on gestational age at trial entry (<28, 28–31, and ≥32 weeks; *P* for interaction = 0.85).

Thus far, no specific randomized controlled trial has assessed the efficacy of magnesium sulfate in patients with clinical chorioamnionitis. Four[210,211,213,215] of the five trials

included in the previously mentioned meta-analyses included a proportion of women with the diagnosis of clinical chorioamnionitis (11–51%); however, results were not reported separately for these women. A subgroup analysis of the IPD meta-analysis showed no clear differences in treatment effects on cerebral palsy among the subgroups of women according to the reason for imminent preterm delivery (preeclampsia, preterm labor, chorioamnionitis, antepartum hemorrhage, and preterm PROM ≥24 hours; *P* for interaction = 0.48).[205] More recently, a secondary analysis of the BEAM trial,[215] which included 1944 women with live, non-anomalous, singleton gestations, assessed separately the effects of antenatal administration of magnesium sulfate on the risk of cerebral palsy among women with (N=228) and without (N=1716) clinical chorioamnionitis.[216] Magnesium sulfate reduced the odds of cerebral palsy in children born to mothers with clinical chorioamnionitis (OR 0.76, 95% CI 0.19–2.76) and in those born to mothers without clinical chorioamnionitis (OR 0.52, 95% CI 0.31–0.86). However, the odds reduction was statistically significant only among children born to mothers without clinical chorioamnionitis. The authors of this study concluded that “antenatal magnesium did not show a clear neuroprotective effect in the setting of chorioamnionitis”.

These results, representing a post-hoc subgroup analysis of the BEAM trial,[215] were not correctly interpreted. Rather, the appropriate question in this study[216] is to determine whether the results in the two subgroups differed significantly from each other. We re-analyzed the data reported in this secondary analysis and calculated a test for interaction to examine whether intervention effects on cerebral palsy and moderate/severe cerebral palsy differ between women with and without clinical chorioamnionitis (Figure 1). The beneficial effect of magnesium sulfate on both cerebral palsy and moderate/severe cerebral palsy did not differ significantly between patients with a diagnosis of clinical chorioamnionitis and those without such diagnosis (*P* for interaction = 0.58 for cerebral palsy and 0.81 for moderate/severe cerebral palsy).

Given that more than 90% of patients with clinical chorioamnionitis deliver within 12 hours of diagnosis with a mean diagnosis-to-delivery interval ranging from 4–8 hours,[6,8,79,99,102,114,190–193] this short interval may cause some clinicians to doubt the efficacy of magnesium sulfate for fetal neuroprotection. However, magnesium sulfate readily crosses the placenta[217–219] and achieves high fetal serum concentrations within 1 hour after the initiation of maternal intravenous administration,[217] which remain elevated to 24 hours in the neonate.[218] In two of the trials that assessed the neuroprotective effects of magnesium sulfate, the median time from magnesium sulfate initiation to birth was 3.7 hours in one trial[211] and 1.6 hours in the other trial,[213] suggesting that magnesium sulfate crosses rapidly to the fetal compartment and that this may confer a neuroprotective effect. Importantly, a subgroup analysis according to the time interval from the first magnesium sulfate dose to delivery in the IPD meta-analysis[205] revealed that the beneficial effect of magnesium sulfate on cerebral palsy did not significantly differ between women with an interval <4 hours and those with intervals 4–11 hours and ≥12 hours (*P* for interaction = 0.77).

In summary, the current evidence supports the administration of antenatal magnesium sulfate to women with clinical chorioamnionitis between 24 0/7 and 33 6/7 weeks of gestation for preventing cerebral palsy in their offspring. It also may be considered for women with a

gestational age between 23 0/7 and 23 6/7 weeks. Delivery should not be delayed in order to administer the full course of antenatal magnesium sulfate for fetal neuroprotection.

Management of labor

Mode of delivery—Once a diagnosis of clinical chorioamnionitis has been established, delivery should be considered, regardless of the gestational age. Clinical chorioamnionitis alone is not an indication for cesarean delivery. Unless contraindicated, induction and trial of labor can be considered. Vaginal delivery is the safer option and cesarean delivery should be reserved for standard obstetric indications. This recommendation is strongly supported by the findings of a large multicenter retrospective cohort study, which evaluated the effect of clinical chorioamnionitis on the risk of adverse maternal outcomes according to mode of delivery.[6] The study included 216,467 women without clinical chorioamnionitis and 4807 women with clinical chorioamnionitis of which 2794 delivered vaginally and 2013 underwent cesarean delivery. Clinical chorioamnionitis, regardless of antibiotic therapy type and duration, was associated with a significantly increased risk of adverse maternal outcomes among women who had a cesarean delivery (adjusted OR 2.31, 95% CI 1.97–2.71), but not among women who had a vaginal delivery (adjusted OR 1.15, 95% CI 0.93–1.43).

Duration of chorioamnionitis and adverse maternal and neonatal outcomes—The time interval between the diagnosis of clinical chorioamnionitis and delivery is not related to the risk of most adverse maternal and neonatal outcomes.[6,8,79,190,192,193,220] In 1994, a study reported that there was no association between the time elapsed from diagnosis of clinical chorioamnionitis to delivery and several adverse neonatal outcomes such as umbilical artery pH <7.20, low Apgar scores at 5 minutes, oxygen requirement, and sepsis.[193] A large prospective cohort study among women who underwent primary cesarean delivery assessed the relationship between duration of clinical chorioamnionitis (diagnosis-to-delivery interval) and adverse maternal and neonatal outcomes.[8] Unadjusted analyses showed that only 3 of 18 outcomes assessed were marginally (uterine atony and Apgar ≤3 at 5 minutes) or significantly (use of mechanical ventilation within 24 hours of birth) associated with the duration of clinical chorioamnionitis. Nevertheless, the absolute increase of these outcomes by each additional hour of chorioamnionitis was very low. A more recent cohort study evaluated the impact of the estimated duration of clinical chorioamnionitis and found that a longer duration did not appear to significantly increase the risk of adverse maternal outcomes.[6] In summary, there is no evidence supporting that immediate delivery after the diagnosis of clinical chorioamnionitis prevents adverse maternal and neonatal outcomes, or long-term neurodevelopmental outcomes. On the contrary, such an approach would lead to an increase in the frequency of cesarean delivery and, therefore, to an increased risk of adverse maternal outcomes.

Labor progression—Women with clinical chorioamnionitis are more likely to have abnormal labor progression or prolonged labor[5,191,221–223] and cesarean delivery for failure to progress or non-reassuring fetal heart rate tracing,[4,5,8,191,192,221–224] and to receive oxytocin for induction or augmentation of labor[191,192,222–224] than those without clinical chorioamnionitis. A large nation-based study showed that women with clinical

chorioamnionitis were 40 percent more likely to have a cesarean delivery than those without clinical chorioamnionitis, after controlling for obstetric and medical confounding variables.[4] It is controversial as to whether chorioamnionitis is the cause or the ultimate effect of dysfunctional labor. Recently, a retrospective cohort study examined the temporal association between the diagnosis of maternal fever in women with suspected clinical chorioamnionitis (N=100) and uterine contractility, measured by an intrauterine pressure catheter, which was placed at least one hour prior to the time of first temperature ≥38°C.[225] This study reported that uterine contractility was maintained for 2 hours after the onset of maternal fever but significantly and steadily declined thereafter, despite no changes in oxytocin dosage. Patients who delivered vaginally (32%) maintained contractility, while those who delivered by cesarean (68%) had diminishing contractility following the onset of fever ($P = 0.01$). Most cesarean deliveries were attributable to arrest of dilatation. Moreover, the responsiveness to oxytocin significantly decreased after the diagnosis of clinical chorioamnionitis. In support of these findings, an in vitro study performed in the early 80s showed that bacteria causing chorioamnionitis, such as anaerobic *streptococcus* species, *Veillonella* species, *Bacteroides* species, and *enterococcus faecalis*, reduce the contractility of human myometrial tissue and its responsiveness to oxytocin during the period of decreased contractility.[226]

In summary, the available evidence supports the hypothesis that clinical chorioamnionitis is associated with reduced uterine contractility. Thus, patients with clinical chorioamnionitis may require higher doses of oxytocin to achieve adequate uterine activity and/or greater uterine activity to effect a given change in cervical dilation.

Continuous electronic fetal heart rate monitoring—Abnormal cardiotocography patterns during labor are significantly more frequent among patients with clinical chorioamnionitis than among those without clinical chorioamnionitis.[191,224,227–229] The most common fetal heart rate (FHR) patterns observed in clinical chorioamnionitis include tachycardia, absence of accelerations, presence of variable and late decelerations, persistently reduced variability, and absence of cycling.[193,228–230] However, none of these patterns have been associated with a significant increase in the risk of adverse neonatal or infant outcomes in pregnancies complicated with clinical chorioamnionitis. A study of 197 women with clinical chorioamnionitis found no association between umbilical artery pH <7.20 and several FHR patterns including loss of variability, absence of accelerations and tachycardia.[193] Another study of 139 patients with intrauterine bacterial infection (defined as clinical chorioamnionitis plus a positive bacterial amniotic fluid culture or neonatal infection) reported that FHR deceleration patterns, decreased variability, and absence of accelerations were not significantly associated with the risk of cerebral palsy at 2 years of age.[228]

Clinical chorioamnionitis has been considered a cause of non-hypoxic fetal compromise. Given that electronic FHR monitoring is a test for fetal hypoxia, its role in clinical chorioamnionitis is less clear.[231] In addition, the benefit of continuous electronic FHR monitoring during labor either in low- or high-risk pregnancies has not been clearly demonstrated.[232] To date, the usefulness of continuous electronic FHR monitoring in the setting of clinical chorioamnionitis has not been assessed in randomized controlled trials.

Despite these issues, most professional and scientific organizations recommend using continuous electronic FHR monitoring during labor in patients with clinical chorioamnionitis.[233–235] This recommendation is largely based upon expert opinion and medicolegal experience. Overall, the management of intrapartum fetal heart rate tracings in patients with clinical chorioamnionitis does not differ from that in patients without clinical chorioamnionitis. It is worth noting that isolated fetal tachycardia is a poor predictor of fetal hypoxemia or acidemia, unless accompanied by minimal or absent FHR variability or recurrent decelerations or both, and is not an indication for immediate operative delivery.

In summary, external continuous electronic FHR monitoring is generally used once the diagnosis of clinical chorioamnionitis has been made and may be used in identifying fetal hypoxic insults so that timely and appropriate action could be instituted to improve perinatal outcome.

Delivery and immediate postpartum period—Women with clinical chorioamnionitis are more likely to have uterine atony, postpartum hemorrhage, and blood transfusion than those without clinical chorioamnionitis.[5–9,223,224,236] Increased frequencies of uterine atony and postpartum hemorrhage appear to be directly related to impairment in myometrial contractility caused by intra-amniotic infection/inflammation.[225] Health professionals who provide obstetric care should be aware that chorioamnionitis is a well-established risk factor for the development of postpartum hemorrhage and should be prepared to manage patients with clinical chorioamnionitis who experience this complication. In addition, interventions that have been shown to prevent and treat postpartum hemorrhage should be readily available in both delivery and operating rooms.

Promising interventions

Vaginal cleansing with antiseptic solutions before cesarean delivery—Evidence from three recent meta-analyses supports that vaginal cleansing with antiseptic solutions before cesarean delivery reduces postoperative infectious morbidity.[237–239] The most recent and comprehensive meta-analysis reported that use of vaginal antiseptic solutions before cesarean delivery significantly reduced the frequency of endometritis, wound infection, and fever when compared to saline solution or no treatment.[239] A subgroup analysis found that vaginal cleansing with antiseptic solutions before cesarean delivery significantly reduced the risk of endometritis in women with ruptured membranes (OR 0.21, 95% CI 0.10–0.44). Subgroup analyses according to the preoperative presence of clinical chorioamnionitis were not reported. A network meta-analysis showed that povidone-iodine 1% had the highest probability of being the most effective treatment for the prevention of endometritis and chlorhexidine had the highest probability for the best agent for the prevention of wound infection.[239–241]

It appears that vaginal antiseptic solutions decrease the risk of endometritis by reducing ascending infection through a reduction of vaginal bacterial load.[242–245] Cleansing the vagina with antiseptic solutions reduces the frequency of endometritis in patients with ruptured membranes even though bacteria may have already ascended and colonized in the uterus prior to cleansing.[182–189] Because most patients with clinical chorioamnionitis who

undergo cesarean delivery have ruptured membranes and are in labor, the use of vaginal cleansing with antiseptic solutions in these women appears to be logical. Further trials are warranted to determine the efficacy of vaginal cleansing with antiseptic solutions before cesarean delivery to reduce the risk of postoperative infectious morbidity in patients with clinical chorioamnionitis.

N-acetylcysteine—N-acetylcysteine (NAC), an antioxidant and anti-inflammatory agent, has been shown to provide substantial neuroprotection against perinatal brain injury in newborn rats.[246–248] A study conducted by our team demonstrated that postnatal dendrimer-based NAC therapy for brain injury suppressed neuroinflammation and led to a significant improvement in motor function of newborn rabbits with cerebral palsy.[249]

Administration of NAC to patients with clinical chorioamnionitis results in rapid placental transfer and predictable NAC plasma concentrations in the fetus.[250] In 2016, the results of a small randomized, placebo-controlled trial that assessed the fetal and neonatal effects of NAC administered antenatally to 22 patients (12 preterm, 10 term) with clinical chorioamnionitis and postnatally to their infants (N=24) were reported.[251] Compared to infants who received saline, infants who received NAC showed beneficial effects such as preserved cerebrovascular regulation, decreased proinflammatory vascular endothelial growth factor, and increased anti-inflammatory interleukin-1 receptor antagonist with no adverse events related to NAC administration.

Recently, the main results of a randomized controlled trial of NAC to prevent adverse neonatal outcome in patients with intra-amniotic infection/inflammation were reported in abstract form.[252] In this study, women with intra-amniotic infection or inflammation diagnosed by transabdominal amniocentesis at 23–33 weeks of gestation were randomized either to NAC 150 mg/kg IV loading dose (60 min), followed by 50 mg/kg IV continuous infusion rate for 4 hours, and followed by 100 mg/kg IV continuous infusion rate until delivery (N=34) or to placebo (N=34). The primary outcome was a composite of mortality and severe short-term neonatal morbidities (grade III/IV IVH, necrotizing enterocolitis grades 2–4, retinopathy of prematurity “grades 2–4”, bronchopulmonary dysplasia, or death). NAC administration was associated with a significant reduction in the frequency of the primary outcome (4/34 [11.8%] vs 13/34 [38.2%]; RR 0.31, 95% CI 0.11–0.85; $P = 0.02$), mainly as a consequence of a reduction in bronchopulmonary dysplasia (1/34 [2.9%] vs 11/34 [32.4%]; RR 0.09, 95% CI 0.01–0.67; $P = 0.02$). There were no significant differences between the study groups in the risk of neonatal sepsis (9/34 [26.5%] vs 12/34 [35.3%]; RR 0.75, 95% CI 0.36–1.54; $P = 0.43$) and newborn death (2/34 [5.9%] vs 6/34 [17.6%]; RR 0.33, 95% CI 0.07–1.54; $P = 0.16$). In summary, the antenatal administration of NAC in patients with chorioamnionitis aiming to reduce neonatal morbidity and mortality is promising, and the beneficial effects reported by these small trials need to be confirmed in future studies.

Algorithm for the management of clinical chorioamnionitis—Based upon the presented evidence, we developed an approach for the management of patients with clinical chorioamnionitis (Figure 2). This approach can be modified as new evidence arises.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Condensation

We examined the available evidence supporting interventions proposed for the treatment of clinical chorioamnionitis, developed a contemporary approach for managing this condition, and identified promising interventions.

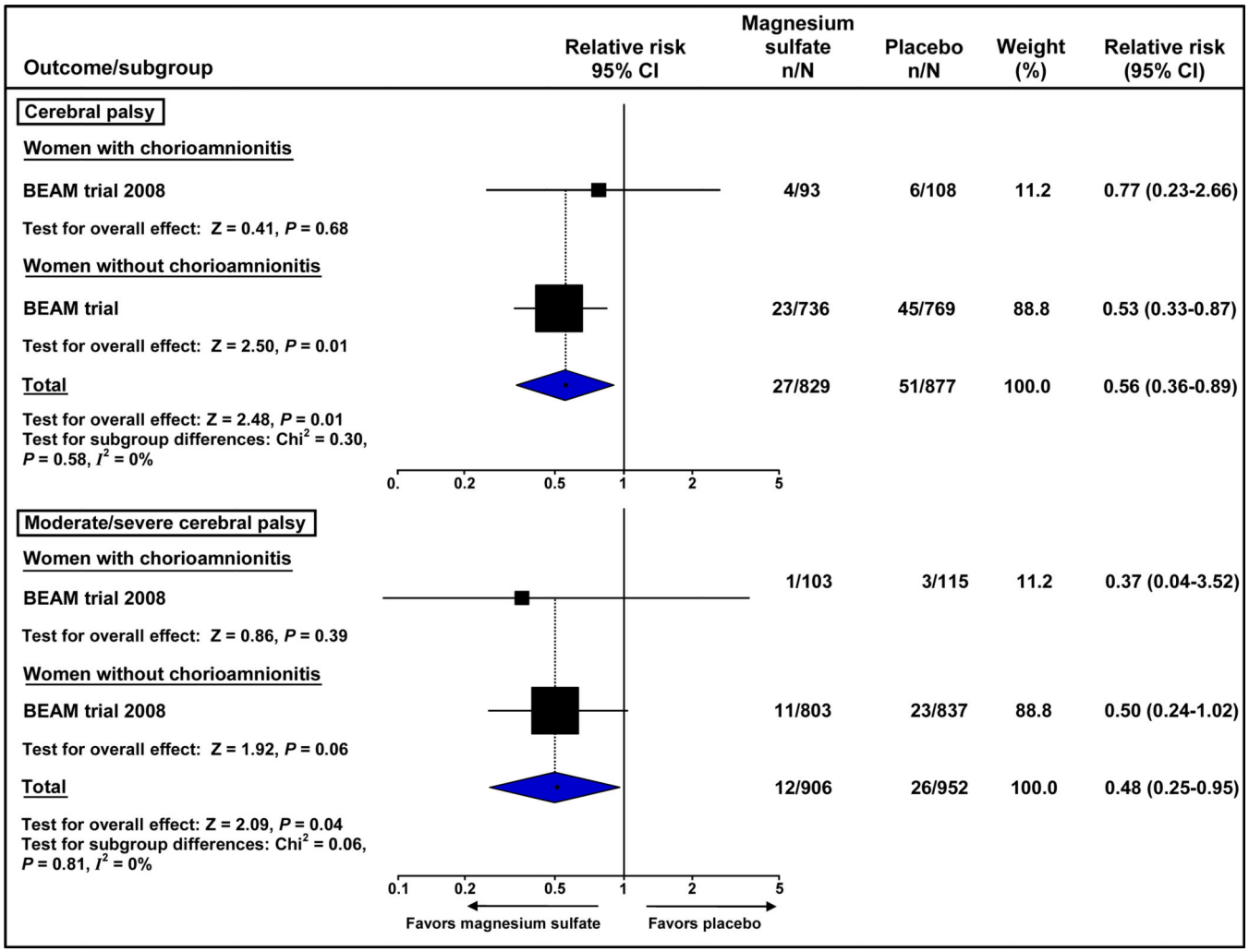

Figure 1.

Effect of antenatal magnesium sulfate on the risk of cerebral palsy and moderate/severe cerebral palsy according to the presence of clinical chorioamnionitis in the BEAM trial[215]

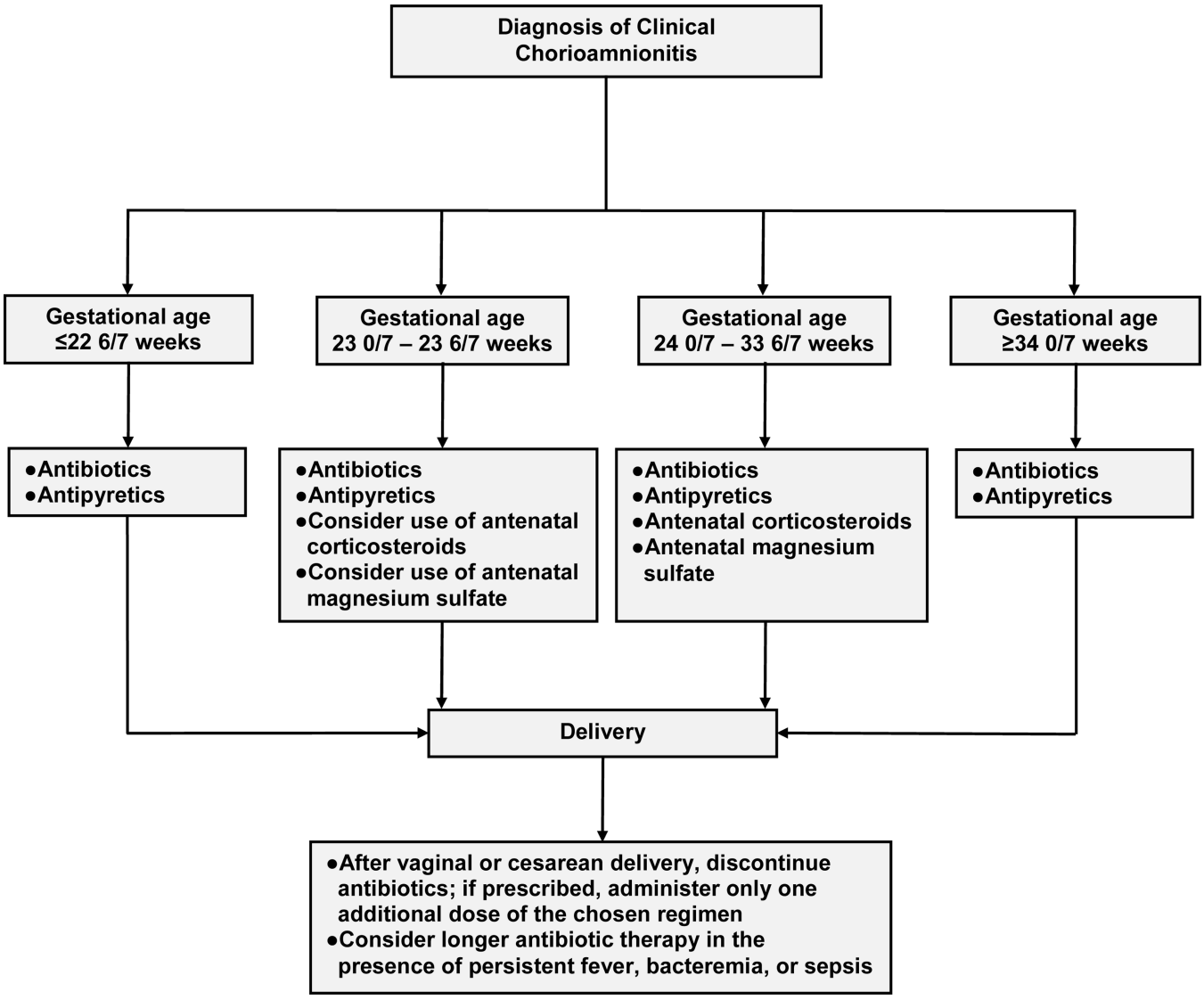

Figure 2.
Proposed approach for the management of clinical chorioamnionitis with a live fetus

TABLE 1

Randomized controlled trials that assessed the use of antibiotics in women with clinical chorioamnionitis

First author, year (country)	Interventions (sample size)	Main outcome (definition)	Main findings
Intrapartum vs. postpartum treatment			
Gibbs, 1988[99] (United States)	(1) Intrapartum treatment: ampicillin 2 g IV every 6 hours and gentamicin 1.5 mg/kg IV every 8 hours, beginning at the time of diagnosis of chorioamnionitis, until afebrile for approximately 48 hours (N=26) (2) Postpartum treatment: ampicillin 2 g IV every 6 hours and gentamicin 1.5 mg/kg IV every 8 hours immediately after cord clamping, until afebrile for approximately 48 hours (N=19) Patients delivered by cesarean section also received clindamycin 900 mg IV every 8 hours, beginning after cord clamping	Neonatal sepsis (bacteremia or death with a clinical diagnosis of sepsis and positive peripheral cultures) and pneumonia	Intrapartum treatment, as compared with immediate postpartum treatment, was associated with a significant decrease in the risk of neonatal pneumonia or sepsis (0.0% vs. 31.6%; RR 0.06, 95% CI 0.000.95; $P = 0.046$), mean neonatal hospital stay (3.8 days vs. 5.7 days; MD −1.9 days, 95% CI −0.4 to −3.4 days; $P = 0.02$), and mean maternal postpartum hospital stay (4.0 days vs. 5.0 days; MD −1.0 days, 95% CI 0.1 to −1.9 days; $P = 0.04$), and a non-significant reduction in the risk of neonatal sepsis (0.0% vs. 21.1%; RR 0.08, 95% CI 0.00–1.44; $P = 0.09$)
Intrapartum treatment			
Scalambrino, 1989[100] (Italy)	(1) Ampicillin/sulbactam 3 g IV every 6 hours for at least 72 h (N=11) (2) Cefotetan 2 g IV every 12 hours for at least 72 h (N=8)	Ineffective treatment (signs and symptoms and/or temperature curve remained unchanged or rose during the first 72 hours of treatment)	Treatment was effective in 100% of women in both antibiotic regimens
Maberry, 1991[101] (United States)	(1) Ampicillin plus gentamicin (dual antibiotic regimen) (N=69) (2) Ampicillin plus gentamicin plus clindamycin (triple antibiotic regimen) (N=64) Dosage not reported. Antibiotics were administered for 24–48 hours after delivery and stopped if the patient remained afebrile	Endometritis	There were no significant differences between the dual antibiotic and triple antibiotic regimens in the risk of endometritis (14.5% vs. 7.8%; RR 1.86, 95% CI 0.67–5.14; $P = 0.23$) and neonatal sepsis (1.5% vs. 3.1%; RR 0.46, 95% CI 0.04–4.99; $P = 0.53$). The frequencies of other adverse neonatal outcomes did not significantly differ between the study groups
Locksmith, 2005[102] (United States)	(1) Ampicillin 2 g IV every 6 hours plus gentamicin 5.1 mg/kg IV every 24 hours (once-daily dosing) (N=18) (2) Ampicillin 2 g IV every 6 hours plus gentamicin 120 mg IV followed by 80 mg IV every 8 hours (thrice-daily dosing) (N=20)	Maternal and umbilical cord serum peak gentamicin concentrations	Median maternal and umbilical cord serum peak gentamicin concentrations were higher with once-daily dosing compared with thrice-daily dosing. There were no significant differences between the once-daily and thrice-daily dosing groups in the risk of puerperal metritis (5.6% vs. 5.0%; RR 1.11, 95% CI 0.07–16.49; $P = 0.94$) and suspected neonatal sepsis (16.7% vs. 25.0%, RR 0.67, 95% CI 0.19–2.40; $P = 0.54$). The frequencies of other adverse maternal and neonatal outcomes did not significantly differ between the study groups
Lyell, 2010[103] (United States)	(1) Ampicillin 2 grams IV every 6 hours for 4 doses total plus oncedaily gentamicin (5 mg/kg IV, then 2 placebo doses IV after 8 and 16 hours) (N=62) (2) Ampicillin 2 grams IV every 6 hours for 4 doses total plus thrice-daily gentamicin (2 mg/kg IV, then 1.5 mg/kg IV after 8 and 16 hours) (N=63) Patients delivered by cesarean section also received clindamycin 900 mg IV every 8 hours, for 3 doses total	Treatment success (resolution of chorioamnionitis after 16 hours of treatment without development of endometritis)	The frequency of treatment success did not significantly differ between the once-daily and thrice-daily gentamicin groups (93.6% vs. 88.9%; RR 1.05, 95% CI 0.94–1.17: $P = 0.36$). Once-daily gentamicin was noninferior to thrice-daily gentamicin because the range of risk difference (5.2% to 14.5%) fell within the predefined margin (15%). There were no significant differences between the study groups in the risk of endometritis (6.5% vs. 7.9%; RR 0.81, 95% CI 0.23–2.89; $P = 0.75$), neonatal sepsis (6.5% vs. 3.2%; RR 2.03, 95% CI 0.39–10.70; $P = 0.40$), and other adverse maternal and neonatal outcomes

First author, year (country)	Interventions (sample size)	Main outcome (definition)	Main findings
Greenberg, 2015[104] (United States)	(1) Ampicillin/sulbactam 3 g IV every 6 hours plus IV normal saline placebo dose every 8 hours until 24 hours postdelivery (N=43) (1) Ampicillin 2 g IV every 6 hours plus gentamicin 1.5 mg/kg IV every 8 hours until 24 hours postdelivery (N=49) Patients delivered by cesarean section also received clindamycin IV (dosage not reported) at the time of umbilical cord clamping, which was continued as part of the antibiotic regimen	Postpartum composite morbidity (any of the following: endometritis, sepsis, pneumonia, blood transfusion or ileus); postpartum infectious morbidity (any of the following: endometritis, sepsis, or pneumonia); and neonatal sepsis	There were no significant differences between the ampicillin/sulbactam and ampicillin plus gentamicin groups in the frequency of postpartum composite morbidity (0.0% vs. 12.2%; RR 0.09, 95% CI 0.01–1.51; $P = 0.09$), postpartum infectious morbidity (0.0% vs. 8.2%; RR 0.13, 95% CI 0.01–2.28; $P = 0.16$), and neonatal sepsis (2.3% vs. 4.1%; RR 0.57, 95% CI 0.05–6.07; $P = 0.64$)
Postpartum treatment			
Berry, 1994[105] (United States)	(1) Ampicillin 2 g IV plus gentamicin 2.0 mg/kg IV at the time of diagnosis of clinical chorioamnionitis. After vaginal delivery, ampicillin 2 g IV every 6 hours for 8 doses plus gentamicin 2.0 mg/kg IV every 8 hours for 6 doses (N=21) (2) Ampicillin 2 g IV plus gentamicin 2.0 mg/kg IV at the time of diagnosis of clinical chorioamnionitis. After vaginal delivery, normal saline on an identical dosing schedule (placebo) (N=17)	Treatment failure (temperature >38 °C after the first postpartum antibiotic or placebo dose)	There was no significant difference between the antibiotic and placebo groups in the frequency of treatment failure (4.8% vs. 5.9%, RR 0.81, 95% CI 0.05–12.01; $P = 0.88$). There were no cases of endometritis, wound infection, or sepsis
Chapman, 1997[106] (United States)	(1) Ampicillin plus gentamicin during the intrapartum period (dosage not reported). After vaginal delivery, cefotetan 2 g IV single dose (N=55) (2) Ampicillin plus gentamicin during the intrapartum period (dosage not reported). After vaginal delivery, cefotetan 2 g IV every 12 hours for at least 48 h (N=54)	Interval from delivery to discharge and failed therapy (any of the following: (1) two temperatures ≥38 °C [single dose group] or ≥38.9 °C [multiple dose group] ≥4 hours apart; or (2) a single temperature ≥38.9 °C >4 hours after delivery [single dose group] or ≥38 °C >24 hours after delivery [multiple dose group]; or (3) postpartum readmission for endometritis)	There was no significant difference between the study groups in the frequency of failed therapy (10.9% vs. 3.7%; RR 2.95, 95% CI 0.62–13.96; $P = 0.17$). The median interval from delivery to discharge was 24 hours shorter in the single dose group (33 hours, range I6–190) than in the multiple dose group (57 hours, range 36–190) ($P = 0.0001$).
Mitra, 1997[107] (United States)	(1) Gentamicin 4 mg/kg IV every 24 hours plus clindamycin 1200 mg IV every 12 hours after delivery (N=65) (2) Gentamicin 1.33 mg/kg IV plus clindamycin 800 mg IV every 8 hours after delivery (N=66) There was no report on antibiotics used in the intrapartum period	Cure (an average temperature of ≤37.2 °C for 24 hours and the resolution of symptoms); failure (a persistently elevated temperature 72 hours after the initiation of antibiotic therapy, clinical deterioration, or the need for additional antibiotic or heparin therapy); and duration and cost of treatment	There were no significant differences between the two treatment groups in the frequency of cure (93.9% vs. 93.9%; RR 1.00, 95% CI 0.92–1.09; $P = 0.98$) and failure (6.1% vs. 6.1%, RR 1.02, 95% CI 0.27–3.89; $P = 0.98$). The group receiving once-daily gentamicin dosing with twice-daily clindamycin dosing had a shorter mean treatment duration (2.0 days) and a lower mean treatment cost (US $251) than the group receiving thrice-daily dosing of gentamicin and clindamycin (2.3 days and US $442, respectively; $P = 0.04$ and 0.0001, respectively)
Adashek, 1998[108] (United States)	(1) Gentamicin plus clindamycin after vaginal delivery. Dosage and duration of treatment were not reported (N=127) (2) Placebo after vaginal delivery (N=123) There was no report on antibiotics used in the intrapartum period	Treatment failure (persistent fever after the third dose of the study drug or readmission for endomyometritis)	There was no significant difference between the antibiotic and placebo groups in the frequency of treatment failure (1.6% vs. 3.3%; RR 0.48, 95% CI 0.09–2.60; $P = 0.40$)
Turnquest, 1998[109] (United States)	(1) Ampicillin 2 g IV every 6 hours. Preoperative gentamicin 2 mg/kg IV plus clindamycin 900 mg IV. After cesarean delivery, gentamicin 1.5 mg/kg IV plus clindamycin 900 mg IV every 8 hours until afebrile for a minimum of 24 hours (N=55) (2) Ampicillin 2 g IV every 6 hours. Preoperative gentamicin 2 mg/kg	Endometritis	There was no significant difference between the postoperative antibiotic and no postoperative antibiotic groups in the risk of endometritis (21.8% vs. 14.8%; RR 1.48, 95% CI 0.68–3.24; P=0.33). The frequencies of other adverse maternal and neonatal outcomes did not significantly differ between the study groups.

First author, year (country)	Interventions (sample size)	Main outcome (definition)	Main findings
	IV plus clindamycin 900 mg IV. No antibiotics after cesarean delivery (N=61)		
Edwards, 2003[110] (United States)	(1) Ampicillin 2 g IV every 6 hours and gentamicin 1.5 mg/kg IV every 8 hours at the time of diagnosis of chorioamnionitis. After delivery, ampicillin 2 g IV plus gentamicin 1.5 mg/kg IV, single additional dose. Patients delivered by cesarean section received clindamycin 900 mg IV single dose at the time of umbilical cord clamping (N=151) (2) Ampicillin 2 g IV every 6 hours and gentamicin 1.5 mg/kg IV every 8 hours at the time of diagnosis of chorioamnionitis. After delivery, ampicillin 2 g IV every 6 hours plus gentamicin 1.5 mg/kg IV every 8 hours until afebrile and asymptomatic for 24 hours. Patients delivered by cesarean section received clindamycin 900 mg IV at the time of umbilical cord clamping, then every 8 hours until antibiotics were discontinued (N=141)	Treatment failure (a single temperature after the first postpartum dose of antibiotics ≥39.0 °C, or two temperatures ≥38.4 °C at least 4 hours apart)	There was no significant difference between the single antibiotic dose and the continued use of antibiotics groups continued antibiotic regimen and the single additional dose groups in the frequency of treatment failure (4.6% vs 3.5%; RR 1.31, 95% CI 0.42–4.02; P = 0.64). The frequencies of wound infection (0.7% vs. 1.3%) and pelvic abscess (0.0% vs. 0.7%) did not significantly differ between the study groups
Shanks, 2016[111] (United States)	(1) Ampicillin 2 g IV every 6 hours and gentamicin 1.5 mg/kg IV every 8 hours until cesarean delivery, plus preoperative clindamycin 900 mg IV. After cesarean delivery, one additional dose of gentamicin 1.5 mg/kg IV and clindamycin 900 mg IV (N=41) (2) Ampicillin 2 g IV every 6 hours and gentamicin 1.5 mg/kg IV every 8 hours until cesarean delivery, plus preoperative clindamycin 900 mg IV. No antibiotics after cesarean delivery (N=39)	Endometritis	There was no significant difference in the frequency of endometritis between women who received one additional dose of antibiotics after cesarean delivery and those who did not receive postoperative antibiotics (9.8% vs. 7.7%; RR 1.27, 95% CI 0.30–5.31; *P* = .74). The frequency of wound infection (17.1% vs. 5.1%, *P* = .12) and median length of hospital stay (4 days vs. 4 days, *P* = .88) did not significantly differ between the study groups. Neonatal outcomes were similar between the two study groups
Goldberg, 2017[112] (United States)	(1) Single antibiotic dose after vaginal delivery (N=23) (2) Antibiotics until afebrile for 24 hours after vaginal delivery (N=23) There was no report on antibiotics used in both intrapartum and postpartum periods	Endometritis	"There were no significant differences for length of stay and no participants experienced treatment failures requiring resumption of antibiotics for endometritis or fevers"

CI, confidence interval; *IV*, intravenously; *MD*, mean difference; *RR*, relative risk

TABLE 2

Alternative antibiotic regimens proposed for the treatment of clinical chorioamnionitis

Antibiotic regimen
Cefotetan 2 g IV every 12 hours[87,100,126]
Cefoxitin 2 g IV every 6 to 8 hours[87,96,97,126,127]
Ceftizoxime 2 g IV every 12 hours[126]
Cefotaxime 2 g IV every 8 to 12 hours[126]
Cefuroxime 1.5 g IV every 8 hours[96]
Cefazolin 1 g IV every 8 hours plus gentamicin 5 mg/kg IV every 24 hours or 1.5 mg/kg IV every 8 hours[96]
Cefuroxime 750 mg IV every 8 hours plus metronidazole 500 mg IV every 8 hours[128]
Mezlocillin 3–4 g IV every 6 hours[126,127]
Piperacillin-Tazobactam 3.375 g IV every 6 hours[87,91,96,126]
Piperacillin-Tazobactam 4 g IV every 6 hours plus clarithromycin 500 mg orally every 12 hours[129]
Ticarcillin-clavulanic acid 3.1 g IV every 6 hours[96,97,126,127]
Ertapenem 1 g IV every 24 hours[10,87]
Meropenem 1 g IV every 12 hours[126]
Imipenem-cilastatin 500 mg IV every 6 hours[126]
IV, intravenously

TABLE 3

Updated meta-analysis of nonrandomized studies assessing the effect of antenatal corticosteroids on adverse neonatal and child outcomes in women with chorioamnionitis

Outcome	No. of studies	Any exposure to antenatal corticosteroids	Non-exposure to antenatal corticosteroids	Pooled odds ratio (95% CI)	*P* value	I^{2},[a] %
Neonatal death						
Histological chorioamnionitis	8[171,173–176,178-180]	150/2071	259/1794	0.45 (0.36–0.56)	<0.00001	18
Clinical chorioamnionitis	3[172,175,176]	17/149	15/98	0.77 (0.36–1.65)	0.50	0
Respiratory distress syndrome						
Histological chorioamnionitis	7[171,173,175,176,178–180]	991/2013	1051/1780	0.66 (0.58–0.76)	<0.00001	0
Clinical chorioamnionitis	4[170,172,175,176]	99/209	99/208	0.73 (0.48–1.12)	0.15	0
Bronchopulmonary dysplasia/ chronic lung disease						
Histological chorioamnionitis	5[175,176,178–180]	802/1676	651/1238	0.78 (0.47–1.31)	0.35	52
Clinical chorioamnionitis	3[172,175,176]	25/142	16/90	0.91 (0.44–1.86)	0.80	0
Neonatal sepsis						
Histological chorioamnionitis	7[171,173,175,176,178–180]	247/2013	266/1780	0.76 (0.63–0.93)	0.006	32
Clinical chorioamnionitis	2[175,176]	26/104	12/46	0.94 (0.40–2.18)	0.88	34
Necrotizing enterocolitis						
Histological chorioamnionitis	7[171,173,175,176,178–180]	90/2013	56/1780	1.13 (0.77-1.65)	0.53	0
Clinical chorioamnionitis	2[175,176]	16/104	3/46	2.63 (0.72–9.68)	0.15	0
Any intraventricular hemorrhage						
Histological chorioamnionitis	7[173-176,178–180]	281/1896	328/1434	0.62 (0.52–0.75)	<0.00001	2
Clinical chorioamnionitis	3[170,175,176]	13/164	20/156	0.37 (0.16–0.83)	0.02	49
Grade III/IV intraventricular hemorrhage						
Histological chorioamnionitis	5[174–176,178,180]	32/472	18/128	0.37 (0.20–0.71)	0.003	0
Clinical chorioamnionitis	3[170,175,176]	5/164	14/156	0.32 (0.03–3.29)	0.34	55
Periventricular leukomalacia						
Histological chorioamnionitis	5[175,176,178–180]	74/1750	72/1378	0.80 (0.57–1.12)	0.19	0
Clinical chorioamnionitis	3[170,175,176]	8/163	24/155	0.35 (0.14–0.85)	0.02	42

Outcome	No. of studies	Any exposure to antenatal corticosteroids	Non-exposure to antenatal corticosteroids	Pooled odds ratio (95% CI)	*P* value	I^2,[a] %
Neonatal seizure						
Histological chorioamnionitis	1[179]	49/1336	80/1264	0.56 (0.39–0.81)	0.002	NA
Patent ductus arteriosus						
Histological chorioamnionitis	4[171,178–180]	597/1654	563/1670	0.92 (0.60–1.41)	0.70	56
Death before 3 years of age						
Histological chorioamnionitis	1[181]	33/438	66/402	0.41 (0.27–0.65)	<0.0001	NA
Cerebral palsy at 3 years of age						
Histological chorioamnionitis	2[174,181]	26/307	18/208	0.93 (0.50–1.75)	0.83	43
Developmental quotient <70						
Histological chorioamnionitis	1[181]	27/189	25/161	0.91 (0.50–1.64)	0.74	NA
Severe hearing impairment						
Histological chorioamnionitis	1[181]	3/247	2/195	1.19 (0.20–7.17)	0.85	NA
Visual impairment						
Histological chorioamnionitis	1[181]	2/246	3/192	0.52 (0.09–3.12)	0.47	NA
Neurodevelopmental impairment						
Histological chorioamnionitis	1[181]	46/194	37/160	1.03 (0.63–1.69)	0.90	NA

CI, confidence interval; *NA*, not applicable

[a]Heterogeneity measure. Fixed-effect model used if I^2 <50%; random-effects model used if I^2 ≥50 Legend for Figures