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Scientific Impact Paper: Understanding Intrapartum Pyrexia: Microbial and Non-Microbial Triggers of Placental Inflammation

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Plain Language Summary

Having a temperature in labour (also known as intrapartum pyrexia or IPP) is common, affecting up to one in 10 parturient women. The causes are varied, and include infection, dehydration, the process of labour itself, medications and regional anaesthesia pain relief (often called 'an epidural'). Identification of the cause is important as treatment may be required, for example giving antibiotics when infection is suspected. In current clinical practice it is often difficult to determine the cause of a temperature in labour. Currently there is no investigation that can reliably assess if an infection is present and guide when antibiotics should be administered.

Blood tests are often performed, such as the white cell count (WCC) and C-reactive protein (CRP), to assess the likelihood of an infection. However, both tests can be abnormal for reasons other than infection, therefore assessment of the whole situation is important (for example, whether a raised heart rate or abdominal pain is also present). Other blood tests such as lactate and procalcitonin have been found to be less helpful in identifying infections and thereby distinguishing infection from other causes of IPP, such as regional anaesthesia or other medications.

In cases of IPP related to both infection and epidurals, inflammation of the placenta is often found but this can only be identified after birth. Although traditional tests can identify most bacteria that can cause placental inflammation, molecular tests (16S rRNA PCR) can now assess a wider range of bacteria that may contribute to IPP. However, the test results can take

time to come back, there is a lack of data on value for money, and the test does not currently influence the management of women in labour. Further work on this is required in the future.

Treatment for IPP commonly includes administration of paracetamol and antibiotics. Antibiotic treatment lowers the risk of severe maternal infection (sepsis), postpartum haemorrhage and uterine infection, and may also lessen the severity of infection in the baby. Consequently, when the temperature is raised (more than 37.5°C on two occasions or more than 38°C on one occasion) these should be administered. Paracetamol is of little or no benefit in improving outcomes for the mother and baby, irrespective of the cause. Steroids have also been evaluated but are of limited benefit in treating the pyrexia and may increase the risk of infection.

1. Introduction

Pyrexia is an elevation of body temperature above the normal daily variation. The National Institute for Health and Care Excellence (NICE) guideline on intrapartum care (NG235) defines maternal pyrexia as a temperature greater than 37.5°C on two occasions, one hour apart, or a temperature on one occasion greater than 38°C.[1] The estimated incidence of intrapartum fever is two to 10%.[2] The scope of this Scientific Impact Paper is confined to the description of the incidence and aetiology of pyrexia in labour. In addition to standard infection work-up, including blood and urine cultures, this paper specifically examines the role of oral, vaginal and placental microorganisms—identified through both conventional culture methods and emerging sequencing technologies—in the pathophysiology of placental inflammation associated with intrapartum pyrexia (IPP).

2. Dilemmas and challenges managing IPP

The first challenge is in the definition of IPP, which varies throughout the literature: Although the UK defines IPP as two readings of more than 37.5°C or one reading of temperature more than 38°C typically measured tympanically, in the USA two readings of more than 38°C or one reading more than 39°C are required.[3] The majority of studies worldwide use a threshold of 38°C.[4]

Causes of IPP are also disparate, encompassing infection, physiological causes and those relating to medication administration and epidural use resulting in further management

dilemmas. All can be associated with chorioamnionitis, a heterogeneous array of conditions characterised by inflammation of the membranes of the placenta that may or may not be infective in aetiology.

Risk stratification and instigation of appropriate labour management, antibiotic and anti-febrile agents, and treatment of the newborn, are all decisions that need to be made. Rapid diagnostic tests for intrapartum infection to help elucidate the underlying cause are currently lacking. Maternal IPP ≥38°C has been associated with a risk of neonatal early-onset group B Streptococcus (GBS) disease of 5.3 per 1000, compared to a background risk of 0.6 per 1000, and maternal pyrexia of 38°C is regarded as a sign of potential infective chorioamnionitis.[3-6] Treatment of fever is justified, but the use of antibiotics in all cases is debatable. The benefit of antibiotics in the absence of a clear focus of infection remains uncertain, particularly where clinical features may reflect an inflammatory response rather than confirmed infection. This distinction is increasingly important given global concerns regarding antimicrobial resistance.[5,7]

The correlation between clinical symptoms of chorioamnionitis (such as fever, tachycardia, and vaginal discharge) and the gold standard test, histopathological evidence of chorioamnionitis from placental assessment post-delivery, is poor[8,9] as is correlation with neonatal outcomes**.** Indeed, placental evidence of chorioamnionitis can be present in approximately 32% with no symptoms in the mother.[2] While epidural analgesia may lead to fever, placental inflammation, and histologic chorioamnionitis, the typical outcomes for both woman and baby are generally favourable. Difficulties in practice arise because there is no diagnostic test for fetal compartment infection during labour.

3. Aetiology of IPP

Specific causes of IPP can be divided into infective, physiological, medication and epidural-related and will be described below:

3.1. Infectious causes

Infectious causes of IPP are predominantly bacterial or viral. Chorioamnionitis (CAM) is an infection of the amniotic fluid, placental membranes, or decidua.[3] It is most often caused by bacteria ascending from the lower genital tract[10], leading to IPP. Traditionally, CAM is suspected when a maternal fever greater than 38.0°C and two or more factors such as

maternal or fetal tachycardia, uterine tenderness, purulent vaginal discharge, or maternal leucocytosis are present**.** However**,** an expert panel (National Institute of Child Health and Human Development, Society for Maternal-Fetal Medicine, American College of Obstetricians and Gynaecologists [ACOG], American Academy of Paediatrics) in 2016, contended that isolated maternal fever is not synonymous with CAM. The panel argued that clinical use of the term chorioamnionitis is outdated and they introduced the concept of 'Triple I', with three different domains. The Triple I concept is currently only used in the USA. It uses three categories: Isolated maternal fever (not Triple I); inflammation without infection (suspected Triple I) and confirmed infection (Confirmed Triple I).[5] In addition, bacterial infection may also arise from other sources such as the urinary or respiratory tracts.

Viral infections, of which respiratory viruses such as such as Covid 19[11,12], influenza and swine flu[12], can also be responsible for IPP. However, these would usually manifest with other symptoms of the underlying pathology e.g., coryzal symptoms, cough or oxygen requirement.

3.2. Physiological causes

Non-infectious factors that may contribute to a rise in maternal temperature include dehydration[5], elevated ambient temperature[5], and the physiological stress of labour.
Mechanical stretch of myometrial cells, as occurs during contractions, increases the expression of multiple cytokines (notably IL-1b, IL-6, IL-8) and chemokines (CXCL8 and CXCL1), and results in elevated levels of pyrogens such as prostaglandin E2 or prostaglandin F2 alpha.[13,14] Transendothelial migration of these inflammatory markers can cause pyrexia in labour.[13,14]

3.3. Medication-related causes

Though not routinely used for the induction of labour in viable pregnancies in the UK, misoprostol is used in other countries for this purpose.[15] Misoprostol is well documented to be associated with fever[16], reportedly due to its effects on the hypothalamus and thermal regulation.[17]

3.4. Epidural-related causes

Labour epidural-associated fever (LEAF) occurs in approximately 10- 25% of women in labour using this form of analgesia.[4,18-21] Although most women receiving epidural analgesia do not experience LEAF, the subset of those who do tend to exhibit signs of temperature increase within 1 to 2 hours of epidural placement.[100] A 2018 Cochrane review highlighted that epidural analgesia more than doubled the fever risk compared to opiates for labour pain management.[22] The increased risk compared to opiates might, in part, be explained by the action of narcotics (low concentrations of opiates inhibit the febrile response).[21] However, the pathophysiological pathway leading to a higher rate of pyrexia with regional anaesthesia in labour remains unclear. Epidural analgesia can affect various human thermoregulatory mechanisms, for example, it has been suggested that by blocking the sympathetic nervous system, both active vasodilation and induced sweating are blocked, which results in heat retention.[19] Compounded with the fact that uterine contractions and metabolic activity of the fetus both increase heat production, there will be a tendency for maternal temperature to increase.[23] In contrast to its effect in labour, it has been reported that sympathetic blockade by epidural anaesthesia in women not in labour can result in hypothermia by redistribution of heat to the periphery and a net heat loss to the environment.[24] Labour and epidural analgesia increase levels of inflammatory markers such as IL-6[25,26] and TNF-α**,** but the mechanism by which this occurs is obscure. Women with epidural analgesia in prolonged labour may have multiple vaginal examinations as an indirect effect, thereby increasing the likelihood of CAM.[29]

4. Placental inflammation

Like the USA consensus group in 2016, the Amsterdam Placental Workshop Group Consensus Statement differentiated acute placental inflammation from amniotic fluid infection (AFI), intrauterine infection (IUI) and ascending infection.[30]

The factors involved in placental inflammation and their association with clinical and histological features are complex. The two main factors associated with the development of IPP due to placental inflammation[1], the role of microbes (vaginal, oral, placental) and epidural analgesia[2] are discussed below:

4.1. Roles of microbes in placental inflammation detected on traditional cultures

Ascending infection from the vagina to the chorioamnion is a possible explanation for adverse maternal and neonatal outcomes.[31] Evidence supporting this shows that bacteria cultured from amniotic fluid samples, obtained through amniocentesis have been found to be vaginal commensals.[32] Group B Streptococcus causes placental inflammation and oxidative stress, reduces trophoblast invasion of endothelial cells, and increases CXCL-8 and IL-6 – key factors that participate in vascular dysregulation observed in several diseases.[33] Bacterial vaginosis (BV) is associated with histologic CAM, neonatal morbidity with a lower median birth weight, higher rate of neonatal intensive care unit admission, increased rate of respiratory distress syndrome and need for invasive respiratory support.[33] The genital mycoplasmas, *Ureaplasma urealyticum* and *Mycoplasma hominis*, constitute the most frequent microbes occurring in 30% of cases of quantitative PCR detected CAM-linked premature rupture of the membranes or CAM.[34-36] Occasionally CAM is the result of haematogenous spread of bacterial or viral infection to the placenta. *Pseudomonas* is very rarely detected and can cause CAM (even with intact membranes) and neonatal death.[37]

4.2. Transforming microbial detection: the imperative for metagenomic sequencing in risk assessment

Established molecular approaches, such as 16S rRNA broad-range PCR, have enabled clinical identification of microorganisms in a polymicrobial sample when compared with traditional culturing methods, also allowing for the identification of unculturable and fastidious microorganisms. New metagenomics next generation sequencing (NGS) technique is a novel culture-independent technique more advanced than 16S rRNA PCR, and allows the identification of multiple microorganisms that may be present in low abundance in a clinical sample mapping the composition of vaginal and placental microbes.

Routinely, two common species – *Streptococcus agalactiae* (GBS) and *Escherichia coli* – are investigated by culture in cord blood samples for early onset sepsis in neonates. However, detection with 16S rRNA PCR techniques showed 99-100% prevalence of *Fusobacterium nucleatum*, a bacteria found in the oral cavity, in paired amniotic fluid/cord blood samples and neonatal gastric aspirates[40] from pregnancies affected by preterm prelabour rupture of membranes as well as those at high risk of preterm birth with intact membranes.

Wang et al. argued that *Fusobacterium nucleatum* should be given the same importance as *Escherichia coli* in developing early onset neonatal sepsis (EONS).[39] The potential mechanism for the spread of oral bacteria during pregnancy is via the haematogenous route[41,42], strengthening the link between periodontal disease and invasion of the placenta.[43] Oral bacteria (*Fusobacterium* species, *Streptococcus thermophilus*) and *Bergeyella* bacteria present in the subgingival plaque infection, are associated with CAM[44] and infection of the amniotic fluid.[40,45]

Doyle et al. found an association between placental and fetal membrane microbiota, inflammation, and birth outcomes, with bacterial DNA in 68·1% of fetal membranes and 46·8% of placental samples. By using 16S sequencing they reported that *Fusobacteria*, *Mycoplasmataceae*, *Leptotrichiaceae*, and *Veillonaceae* were all found in placental tissues when there was severe CAM in the fetal membranes.[31]

Rapid (six hour) metagenomic next-generation sequencing is being explored as a diagnostic adjunct in selected cases of pneumonia and sepsis[87,88], particularly where conventional cultures are negative, although it is not yet in widespread routine clinical use. Successful use of nanopore sequencing, a long-read, real-time DNA sequencing technique, to diagnose intraamniotic infection within 5-9 hours has been recently reported.[94]

Table 1: Placental microbiota detected by rapid next-generation sequencing: implications for pregnancy outcomes.

	Chorioamnionitis	**Early onset neonatal sepsis**	**Smaller newborn size / lower newborn head circumference**
Vaginal microbes on placenta	*Lactobacillus jensenii* *Prevotella bivia* *Prevotella* spp *Atopobium vaginae* *Finegoldia magna* *Aerococcus christensenii*	*Streptococcus agalactiae** *Escherichia coli**	*Sneathia sanguinegens* *Prevotella copri* *Lachnospiraceae* spp *Phascolarctobacterium succinatutens*[31]
Oral microbes on placenta	*Fusobacterium* spp *Streptococcus thermophilus* *Bergeyella* spp	*Fusobacterium nucleatum*	

4.3. Feasibility of current and future prediction and prevention tools

Early identification of IPP and intraamniotic infection is critical, as intervention may be delayed until fever or clinical signs become apparent, potentially compromising maternal and

neonatal outcomes. The development of robust prediction and prevention tools is essential to shift from reactive to proactive management in obstetric care. 'Alpha diversity'— which refers to the variety of different microbes present in a sample — has been strongly linked to the severity of CAM.

Existing tools such as the Sepsis 3 / quick Sepsis-Related Organ Failure Asessement (qSOFA), Systemic Inflammatory Response Syndrome (SIRS) criteria, Sepsis in Obstetrics Score (SOS), and the Kaiser Permanente Sepsis Risk Calculator (KP SRC), provide valuable risk assessment frameworks. However, integrating advanced techniques, particularly next-generation sequencing, could significantly enhance prediction accuracy and enable targeted prevention strategies. Further research is required to validate these approaches, ensuring their clinical applicability and seamless incorporation into obstetric guidelines. The feasibility of current and future predictor tools, which might be incorporated into clinical settings, is shown in **Table 2**.

Table 2: Critical analysis of current and possible future predictor tools.

Current predictor tool	**Critical analysis**
Systemic Inflammatory Response Syndrome (SIRS) criteria Combination of temperature ≥38°C plus any one of: • heart rate ≥100bpm • respiratory rate ≥20 breaths/minute • systolic blood pressure <100 mmHg, or • white cell count >16.9 × 109/L^3	International consensus group (97) criticised SIRS criteria as a poor predictor of infection, however the presence of bloodstream infections in 2-3% of mother–newborn pairs means that it may still be prudent to initiate antibiotics in these patients[3,89]
Sepsis in Obstetrics Score (SOS) An SOS ≥6 was independently associated with increased intensive care unit admissions, positive blood cultures, and fetal tachycardia[10,90]	An SOS ≥6 (maximum score 28) has a sensitivity of 88.9%, specificity of 95.2%, positive predictive value of 16.7%, and negative predictive value of 99.9% for intensive care unit admission[10]
The Kaiser Permanente Sepsis Risk Calculator (KP SRC)	The validated neonatal 'sepsis calculator' guide for antibiotic use in late preterm and term neonates born to mothers who

https://neonatalsepsiscalculator.kaiserpermanente.org[91]	had IPP. This is widely used in the UK as a guide for antibiotics administration
Future predictor tool	**Critical analysis**
Mathematical prediction (nomogram) Uses seven risk factors to identify women at high risk for developing intrapartum fever: 1. nulliparity 2. prolonged rupture of membranes 3. estimated fetal weight 4. epidural analgesia 5. second stage duration>120min 6. analgesia duration **7.** amniotic fluid pollution grade III (yellowish-brown, viscous amniotic fluid combined with yellowish fetal membranes)[92]	This nomogram can help obstetricians predict and prevent IPP. Women with a score of 167 or more are at high risk for developing intrapartum fever
Predictive CAM (PCAM) score	PCAM in its simplest form, is based on counting the bacterial species with a proportional abundance cut-off value of 1.5. Scores ≥2 and ≤1 are defined as PCAM-positive and PCAM-negative, respectively[93] PCAM score had the highest predictive accuracy for the diagnostic criteria of CAM and the therapeutic threshold as compared to body temperature, heart rate, white blood cell count, C-reactive protein value and cervical length in cases of suspected preterm labour

4.4. The role of epidural anaesthesia in placental inflammation

Several studies[25,46,47,48] and a systematic review[49] concluded that epidural analgesia is associated with maternal intrapartum fever, placental inflammation and histological CAM. However, two cohort studies[50,51], a recent systematic review and metanalyses[4,18] did not find a link between labour epidural-associated fever and adverse neonatal outcome. Vallejo et al[53]

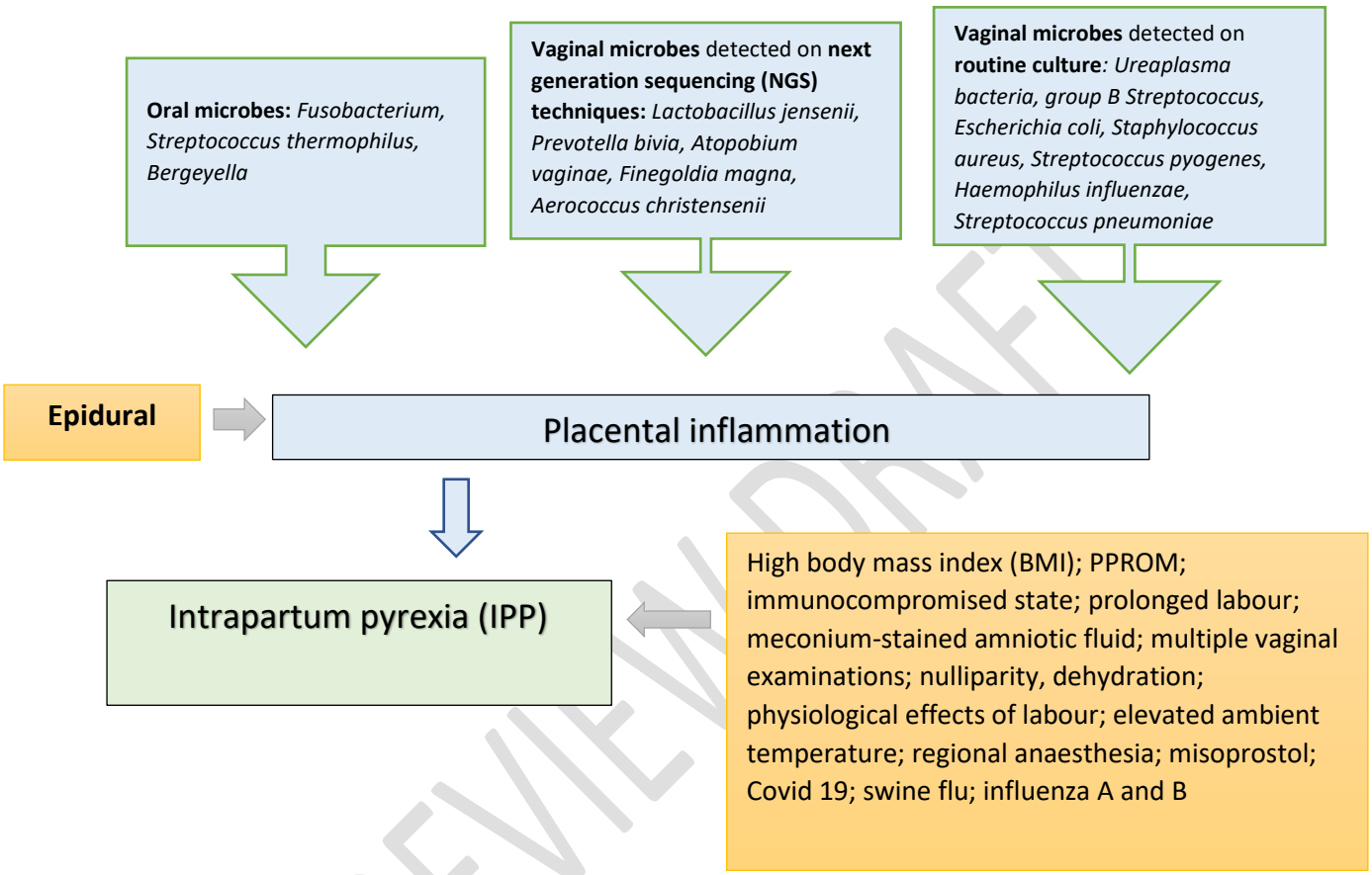
reported that labour epidural analgesia without concomitant CAM was not associated with elevated maternal fever.

The exact mechanism linking epidural anaesthesia and histological CAM is not known. However, the connection between epidural-related fever and neutrophilic placental inflammation[70], as well as the link between fever during labour and non-infectious placental CAM[25,26], might explain this observation.

Table 3: Epidural analgesia, vaginal and oral microbes-related adverse outcomes.

	Fever	Placental inflammation	Histological CAM	Early onset neonatal sepsis	Stillbirth	Preterm labour/ preterm prelabour rupture of membranes (PPROM)
Vaginal microbes	↑	↑	↑	↑	↑	↑
Oral microbes	↑	↑	↑	↑	↑	↑
Epidural	↑	↑	↑			

Figure 1: Microbial and non-microbial triggers of placental inflammation.



5. Clinical assessment

History should be taken to assess the causes of infection and check consciousness, pain, colour of skin, mottled or ashen appearance, cyanosis or rash. Maternal observations (pulse, blood pressure, respiratory rate, oxygen saturation and urine output) should be recorded on modified early warning score for obstetrics (MEOWS) charts. These help the identification of red flags and early detection of the deteriorating patient, prompting staff to escalate using the SBAR (situation, background, assessment, response) tool. An examination should include palpation of the uterus (to assess frequency and duration of contractions, tenderness) along with vaginal examination (to assess foul smelling or purulent discharge and dilatation of the cervix).

6. Investigations currently used in clinical practice

Contemporaneous diagnosis of an infective or epidural-related IPP is currently challenging. Although amniotic fluid culture and blood cultures can identify infective pathogens, these typically take three days to process and have limited utility in the acute setting of labour management. The WCC is often used as a more immediate marker to evaluate for the presence of infection. C-reactive protein (CRP) is an acute-phase protein that shows increased expression in the presence of infection, injury and inflammation. The median value of CRP intrapartum is between 0.2 and 0.8 mg/dL (2mg/L and 8mg/L)[20], which rises to 1.12 mg/dL (12mg/L) for CAM and neonatal infection.[54,55] A study reported significant variability in CRP values during the immediate postnatal period, with over 21% of healthy women exhibiting CRP levels >100 mg/L on the day following a caesarean birth.[56]

The procalcitonin test (PCT) is a biomarker regarded as specific for bacterial infections. Although one study found 94.6% of women had normal PCT levels at the time of septic screening[57], another reported PCT as the most reliable predictor of blood culture positivity.[58] A cut-off level of <0.1 ng/ml was associated with a low risk of bacteraemia, whereas PCT was 8.5-fold higher in association with positive blood cultures.[58] Dockree et al. recommend using values of a single PCT level ≥0.5 ng/mL regardless of body mass index (BMI), blood pressure or maternal age to help diagnose suspected sepsis or guide antibiotic therapy in women at any stage of pregnancy.[59]

During the second stage of labour, factors such as exertion, dehydration, haemorrhage, and the natriuretic effects of oxytocin can elevate maternal lactate levels.[60] Lactate levels above 2 mmol/L are generally considered abnormal in pregnant women, similar to the non-pregnant population.[85] NICE guidelines[101] recommend a 2 mmol/L threshold to identify patients for potential antimicrobial therapy, though this lower threshold has a specificity of only 59.2% for infection in labour or postpartum[60] leading to possible diagnostic ambiguity. In contrast, lactate levels above 4 mmol/L remain uncommon in pregnant women, with a specificity of 95.3% and no ambiguity in the management. Hence guidelines suggest that a maternal lactate >4 mmol/L indicates life-threatening tissue hypoperfusion and potential end-organ damage, warranting immediate treatment with intravenous antibiotics and fluid resuscitation.[71,72]

Unlike CRP and WCC, procalcitonin is a highly specific marker for bacterial infection not yet incorporated into routine obstetric practice. However, it may hold potential as a tool for

guiding antibiotic decisions and, like lactate, serve as a marker of severity and prognosis in pregnancy-associated sepsis.[60,85]

7. Management

Antipyretics, antibiotics and antiseptics

In 2019, NICE concluded that there is no strong recommendation for the use of paracetamol in IPP, and its use is not a suitable treatment for sepsis. In addition, it should not delay suspected sepsis investigation.[61] It may reduce maternal discomfort but has no clinical benefit in terms of reducing caesarean delivery rate or neonatal intensive care unit admission.[61-63] A 2021 systematic review and metaanalysis by Morton et al[4] concluded that in addition to infective causes, epidural analgesia (n=39 studies) is associated with IPP, and IPP is associated with adverse neonatal brain injury (n=31 studies). Two mechanisms have been proposed for the association between intrapartum hyperthermia and neonatal brain injury: the cytokine hypothesis[95] and the energy failure hypothesis[96], neither of which is fully proven.

The cytokine hypothesis suggests that intrauterine infection induces a neurotoxic inflammatory response in the fetus. The energy failure hypothesis posits that hyperthermia exacerbates neuronal injury by increasing intracellular energy deficits after an intrapartum insult. This hypothesis underpins the use of therapeutic hypothermia for treating neonates with hypoxic-ischaemic encephalopathy.[97] While the cytokine hypothesis appears specific to CAM, the energy deficit hypothesis is applicable to any intrapartum hyperthermia. The meta-analysis[4] finding that intrapartum hyperthermia, regardless of cause, is associated with neonatal brain injury supports this argument. Therefore, addressing the prevention of epidural-induced hyperthermia appears to be a prudent strategy. In this regard, Mullington et al[63] concluded that paracetamol does not prevent epidural hyperthermia. Furthermore, a randomised, double-blind, placebo-controlled study[64] reported no effect of prophylactic paracetamol administration on the development of maternal fever immediately after epidural.

Prophylactic epidural methylprednisolone administration (80mg) was also ineffective in reducing intrapartum fever or neonatal inflammation.[65] Randomised trials showed that high-dose intravenous methylprednisolone prevented maternal temperature elevation[65] and the addition of low-dose dexamethasone to the epidural maintenance solution mitigated

increases in maternal temperature.[66] However, high-dose intravenous methylprednisolone increased the risk of asymptomatic bacteraemia in the neonate.

Chlorhexidine is considered to be effective against vaginal dysbiosis and against biofilms produced by bacteria without affecting gestation,[40] but there is no evidence to support the use of vaginal chlorhexidine during labour to prevent maternal and neonatal infections.[67]

Also, a Cochrane review does not support the use of vaginal disinfection with chlorhexidine in labour for the prevention of early onset GBS morbidity in preterm and term infants.[68]

8. Treatment with antibiotics

A randomised trial[70] of prophylactic antibiotic use to prevent epidural-induced pyrexia and a review by Mullington et al[63] reported no benefit. The NICE committee[69] and ACOG (Intrapartum Management of Intraamniotic Infection Committee)[71] acknowledge that, unlike maternal GBS colonisation, clinical CAM, preterm labour or persistent temperature elevation, limited data exist to guide the management of women with isolated IPP. In the absence of guidance, clinicians often choose to treat because prophylactic antibiotics reduce maternal sepsis, pelvic infection, postpartum haemorrhage and endometritis.[69,71] Initiation of intrapartum antibiotic therapy may also reduce the frequency and severity of neonatal infection.[69] However, this can lead to allergic reactions, early separation of the baby from the mother, maternal stress/anxiety, and maternal anaphylaxis, which has a significant impact on fetal oxygenation, leading to hypoxic-ischaemic encephalopathy, permanent neurological damage, or even fetal death[5]. Both ACOG[71] and the Royal College of Obstetricians and Gynaecologists[72] recommend consulting the local microbiology laboratory and infectious disease experts to ascertain whether there are alternative recommended regimens based on local antibiotic resistance patterns.

Cefuroxime and clindamycin are no longer part of many hospital formularies because of their association with *Clostridium difficile*. Cefazolin is recommended by ACOG for the prevention of group B Streptococcal early-onset disease[71] in newborns in low-risk penicillin allergic cases. It is also endorsed by the RCOG for the management of suspected bacterial sepsis during pregnancy.[72]

Histopathologic evaluation of the placenta in the context of isolated fever/suspected or confirmed infections can be useful, together with cultures from the placenta on both maternal and fetal sides. However placental cultures from the maternal side can give false positive results owing to contamination during delivery.

9. Fetal monitoring

Chorioamnionitis does not correlate with any specific characteristic cardiotocograph (CTG) abnormalities other than a rise in the baseline, which should be considered a suspicious feature. In the hypoxic pathway, an increase in fetal heart rate (FHR) is catecholamine-mediated and occurs to protect the myocardium. In intrauterine infection, a rise in baseline FHR is secondary to inflammatory mediators and raised metabolic rate secondary to ongoing inflammation, which can occur without preceding decelerations.[73,74] In addition, in term fetuses with a strong vagal dominance, intrauterine infection may not increase the baseline heart rate above 160 bpm.[73]

In a UK study[75] with confirmed cases of CAM, analysis showed that 100% of CTG traces showed a > 10% increase in the baseline FHR.

In another study by Galli et al, persistent loss of accelerations (64.3%), chemoreceptor-mediated decelerations (63.5%), and baroreceptor-mediated decelerations (46.6%) were the most common abnormal findings in the 'chorioamnionitis' group (n=356). Loss/absence of variability (30.9% cases) was associated with meconium-stained amniotic fluid (MSF) and lower umbilical cord arterial and venous pH ($p < 0.01$ for both).[73] More than a 10% rise in baseline and loss of cycling with or without tachysystole[75] can therefore be considered a feature of CAM. Similarly, more than a 10% rise in baseline during labour without preceding CTG signs of hypoxia, in the absence of maternal pyrexia, is associated with CAM[73]**.**

While there is no evidence suggesting that using a fetal scalp electrode increases the risk of neonatal sepsis in the IPP/ intraamniotic infection setting, it is prudent to use it only when an external device does not provide adequate information. It is better to avoid fetal blood sampling because neurological injury in fetuses is more commonly due to inflammatory mediators than hypoxic pathways and so a normal pH may give false reassurance.

10. Mode of delivery

There is a clear association of IPP and intraamniotic infection with dysfunctional labour.[14,76] One study showed that a first stage of labour exceeding 720 min was significantly associated with the development of maternal fever, and the mean length of the second stage of labour was significantly longer in the febrile group, exceeding 120 min.[62] In the presence of fever, higher doses of oxytocin are required to achieve adequate uterine activity.[14,62] Furthermore, caesarean birth in the presence of intraamniotic infection increases the risk of wound infection, endometritis, venous thrombosis and future increased risk of uterine rupture with a trial of labour after caesarean birth.

11. Neonatal management

Maternal pyrexia is associated with potentially serious maternal and neonatal complications. Infant complications associated with intraamniotic infection include early onset neonatal sepsis (EOS), pneumonia, meningitis, intraventricular haemorrhage, periventricular leukomalacia, and risk of long-term sequelae such as asthma and cerebral palsy. [14,56,77-79]

Initiating antibiotic treatment in neonates born in the context of CAM is based on a combination of clinical and biochemical factors and requires a good communication between maternal and neonatal teams. The actual intrauterine transmission of microorganisms to the fetus is very low, and treating every exposed neonate would increase the neonatal exposure to antibiotics possibly prolonging their hospitalisation. Different scores have therefore been developed with the aim to identify those newborns at higher risk of early infection. In the UK, some NHS hospitals use the KP SRC, which according to Goel N et al[77] could potentially reduce interventions and antibiotic usage in three out of four infants and promote earlier discharge from hospital in >50% of cases. The study did not identify any EOS cases missed by SRC compared with NICE guidance. In view of the theoretical possibility of missing additional cases using this calculator compared to NICE guidance[80], large scale studies have been performed before introducing the use of SRC in a different geographical context where the incidence of GBS infection and EOS vary.[81] Risk stratification might benefit from the combination of risk scores and bio-markers, like the increased levels of IL-6 and procalcitonin in venous cord blood associated with histological CAM and adverse neonatal and infantile outcomes, as identified by Horinouchi T et al. [82]

On a practical level, the main tools currently available to support healthcare professionals in the clinical assessment of the baby and to facilitate decision making include NICE guidance, the KP SRC and the Newborn Early Warning Track and Trigger (NEWTT2) tool (see **Table 2**). These tools help health professionals navigating possible different scenarios, some examples include:

a) Intrapartum maternal pyrexia >38^{0}C in an otherwise well baby

The NICE guideline highlights, as a non-red flag risk factor for neonatal infection, the presence of intrapartum maternal pyrexia >38^{0}C with suspected or confirmed maternal bacterial infection. If no other antenatal risk factors are identified (Box 1), the baby can receive midwifery assessment at birth followed by routine postnatal care. The NICE guideline suggests the use of clinical judgement in determining the frequency of postnatal observations, and the use of NEWTT2 when monitoring continues beyond the first 12 hours of life. In babies ≥ 34 weeks, the KP SRC can be used to further define and stratify the risk of infection and guide appropriate management, taking in consideration for example, the exact maternal temperature.

The presence of another red- or non-red flag risk factor at birth (Box 1) will instead trigger clinical review, testing and initiation of antibiotics treatment. The KP SRC can again represent a useful tool in babies ≥ 34 weeks. As mentioned, this risk score will not be applied in case of neonatal GBS disease in a previous pregnancy.

Box 1 Risk factors for early-onset neonatal infection, including 'red flags', as per NICE guideline NG195.[20]

Red flag risk factor
• Suspected or confirmed infection in another baby in the case of a multiple pregnancy
Other risk factors (non-red flag)
• Invasive group B Streptococcal infection in a previous baby or maternal group B Streptococcal colonisation, bacteriuria or infection in the current pregnancy • Preterm birth following spontaneous labour before 37 weeks of gestation • Confirmed rupture of membranes for more than 18 hours before a preterm birth • Confirmed prelabour rupture of membranes at term for more than 24 hours before the onset of labour • Clinical diagnosis of chorioamnionitis

b) Intrapartum maternal pyrexia >38^{0}C associated with other clinical indicators of possible neonatal infection

When IPP >38^{0}C is associated with one or more clinical indicators of possible early-onset neonatal infection (Box 2), the neonatal team should be informed as clinical observation and monitoring might not be enough. In babies < 34 weeks, prompt review and initiation of antibiotic treatment will be required. In babies ≥ 34 weeks, thorough examination combined with the KP SRC will provide guidance on appropriate management. When close monitoring is indicated, NEWTT2 can be used.

Box 2: Clinical indicators of possible early-onset neonatal infection, as per NICE guideline NG195.[20]

Red-flag clinical indicators	
• Apnoea • Seizures • Signs of shock	• Need for mechanical ventilation • Need for cardiopulmonary resuscitation
Other clinical indicators (non-red flag)	
• Altered behaviour or responsiveness • Altered muscle tone (for example, floppiness) • Feeding difficulties (for example, feed refusal) • Feed intolerance, including vomiting, excessive gastric aspirates and abdominal distension • Abnormal heart rate (bradycardia or tachycardia) • Signs of respiratory distress (including grunting, recession, tachypnoea) • Hypoxia (for example, central cyanosis or reduced oxygen saturation level) • Persistent pulmonary hypertension of newborns • Jaundice within 24 hours of birth • Signs of neonatal encephalopathy • Temperature abnormality (lower than 36°C or higher than 38°C) unexplained by environmental factors • Unexplained excessive bleeding, thrombocytopenia, or abnormal coagulation • Altered glucose homeostasis (hypoglycaemia or hyperglycaemia) • Metabolic acidosis (base deficit of 10 mmol/litre or greater)	

While postnatal antibiotic treatment has reduced morbidity and mortality in EOS, the long-term effect of antibiotic exposure is not fully understood. Possible side effects of antibiotics include the disruption of the child's gut microbiome composition and maturation, resulting in higher risk of allergies and other diseases of adult-onset such as gastrointestinal disorders, eczema, immune system disorders and asthma. A better understanding of antibiotic mechanism of action might also guide appropriate choice of treatment; ampicillin and gentamycin have, for example, the least effect on neonatal gut microbe flora.[77] Intrapartum

antibiotics can equally cause vaginal dysbiosis and reduction of core species, like *Lactobacillus spp*, altering the neonatal environment during birth.

Once postnatal anti-microbial therapy is started, evidence to guide the duration of treatment is limited. In the context of low clinical suspicion of infection, the NICE guidelines suggest stopping antibiotics at 36 hours if the blood culture remains negative and other biochemical markers are reassuring (e.g. PCR). The recommendation is to otherwise prolong the treatment for a total of 7 days in case of positive blood culture or strong suspicion of infection. Treatment might be extended further in more complex scenarios, including meningitis.[20]

12. Continuation of a therapeutic dose of antibiotics post-delivery

Maternal antibiotics in the postpartum period should be guided by persisting risk factors such as fever, suspicion of infection or deteriorating inflammatory markers. Commonly, after caesarean or instrumental birth, a single dose of intravenous antibiotic is sufficient.[84]

13. Opinion

- Clinically, maternal fever is often regarded as almost synonymous with CAM; but isolated IPP should be distinguished from suspected or confirmed intraamniotic infection.
- Epidural analgesia is associated with maternal IPP and non-infectious placental inflammation. However, antibiotics, pre-epidural prophylactic steroid administration and prophylactic paracetamol administration immediately after epidural placement to prevent fever are not recommended.
- We anticipate that molecular microbiologic techniques, such as 16S rRNA broad-range PCR and nanopore sequencing—a long-read, real-time DNA sequencing method—will eventually replace traditional culture methods. These advancements will enable the identification of new bacterial species; development of new tools to enhance prediction and prevention of IPP, intraamniotic infections and guide the selection of appropriate antimicrobial agents for mothers and neonates in the future.
- Historically, the focus of intraamniotic infections in the UK has been on detecting group B streptococcus, mycoplasma, and *E. coli* organisms (via routine culture or

postnatal cord bloods) and treatment. New research on other microbes causing placental inflammation could expand this focus. Understanding these factors may lead to better prediction tools and antibiotic guidelines, reducing unnecessary treatments and evaluations for sepsis given the fear that infection will be missed.

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[Please note that the references have not been formatted yet]

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Appendix 1: Neonatal clinical assessment tools.

On a practical level, the main tools currently available to support healthcare professionals in the clinical assessment of the baby and to facilitate decision making include:

1. NICE guidelines

Recommendations developed by NICE for the treatment and prevention of early onset neonatal infection. Regularly updated based on current evidence.[83]

2. Kaiser Permanente Sepsis Risk Calculator (KP SRC)

Used in babies born at ≥ 34 weeks of gestation to estimate the baseline risk of sepsis at birth. The KP SRC relies on a multivariate model based on a combination of different factors – maternal pyrexia, gestational age at birth, timing of rupture of membranes, maternal GBS status, type and timing of intrapartum antibiotics. The calculation can be repeated within < 12 hours of age if new information becomes available.

An elevated SRC score indicates the need for the midwife to request a clinical review from the neonatal team. Appropriate patient management will then be defined, based on baby clinical status defined as: well-appearing, equivocal, clinical illness.

The combination of the calculated baseline risk and the patient's clinical status will determine if the baby requires:

- routine observations
- enhanced observations, which can be completed using NEWTT2 (usually every 4 hrs for 24 hrs)
- laboratory investigations followed by enhanced observations
- laboratory investigations followed by immediate initiation of antibiotic treatment.

The KP SRC cannot be applied in case of neonatal GBS disease in a previous pregnancy, and NICE guidelines will need to be followed [98].

3. Newborn Early Warning Track and Trigger (NEWTT2) tool

Early warning tools have been used in adult and paediatric setting for a number of years. They encompass observation charts designed to guide healthcare professionals in a structured assessment of the patient's condition. Their use is recommended in at-risk groups where early detection of clinical changes is key to trigger escalation of care and guide appropriate management. The tool has been regularly updated, and in its most recent version includes parental concern to acknowledge the importance of the opinion of the family in addition to the wider multi-disciplinary team[99].