NICE National Institute for Health and Care Excellence

2022 exceptional surveillance of neonatal infection: antibiotics for prevention and treatment (NICE guideline NG195)

Surveillance report
Published: 27 September 2022

www.nice.org.uk

Contents

Surveillance decision

We will not update the recommendations about the use of gentamicin for early onset neonatal infection in NICE's guideline on neonatal infection at this time.

Reason for the exceptional review

We received an enquiry from an NHS microbiologist about a lack of recommendations in the NICE guideline about when to start treatment with neonatal gentamicin for suspected sepsis if the neonate has already been administered gentamicin during labour. The enquirer raised concerns that in practice gentamicin may be being administered to neonates with already elevated gentamicin serum levels transferred from mother during labour with the risk of ototoxicity. They noted this lack of clarity in the NICE guideline is causing confusion in practice about when to commence gentamicin immediately in neonates versus when to check the gentamicin serum level before commencing treatment.

Reasons for the decision

We found limited evidence that neonates exposed to gentamicin *in utero* have raised gentamicin serum levels if the interval between exposure and birth is very short. This does not warrant a change of recommendations as it included only a small number of babies born very soon after exposure.

Additionally, topic experts indicated that the serum levels of gentamicin resulting from an intrapartum dose are unlikely to be high enough at birth to place a neonate at risk of toxicity if a neonatal dose subsequently needs to be given. Experts expressed concern that adding recommendations to measure gentamicin serum concentration levels in neonates before giving a first post-birth dose of gentamicin for early onset infection could delay treatment. As treatment of early onset neonatal infection is often time-critical, topic experts felt any treatment delays presented a greater risk than accidental overdose.

Methods

The exceptional surveillance process consisted of:

- Feedback from topic experts about whether they thought there was a gap in the NICE guideline about intrapartum gentamicin doses. We also asked for their comments on potential editorial amendments to address the issue.
- A focussed search of PubMed to identify any literature about gentamicin blood cord levels and serum levels in neonates exposed to gentamicin *in utero*.
- Internal clinical feedback from within NICE about the enquiry.
- Considering the enquiry that triggered the exceptional review.
- Considering the evidence used to develop the guideline in 2021.
- Examining the NICE event tracker for relevant ongoing and published events.
- Assessing the new evidence and topic expert feedback against current recommendations to determine whether or not to update sections of the guideline.

We decided that full updated literature searches were not needed because the information we had from topic experts and from a focussed search of PubMed was enough to establish whether an update to the guideline recommendations was needed.

For further details about the process and the possible update decisions that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

Information considered in this exceptional surveillance review

Discussion of the evidence

PubMed searches for cord concentrations of gentamicin and *in utero* exposure to gentamicin highlighted a lack of evidence. We identified 1 randomised controlled trial (RCT; Locksmith et al. 2005; n=38 labouring women) that investigated maternal and foetal gentamicin serum concentration and clearance rates. It compared gentamicin 5 mg per kg every 24 hours ('once daily'; dose range 280 mg to 410 mg) with a loading dose of 120 mg followed by 80 mg every 8 hours ('standard'). It reports peak cord levels for the once daily group (the regimen closest to that recommended by the NICE guideline) of 6.5 micrograms / ml (based on 3 births within 1 hour of administration) and a half-life of

5.6 hours. The study observed a rapid drop in foetal serum concentration with increasing time interval from mother's last dose for both groups, although a slightly slower rate of decline was noted for the once daily regimen.

The study made estimates based on extrapolation from a line of best-fit curve which suggested cord clearance of gentamicin to a concentration of less than 2 micrograms / ml (equivalent to 2 mg / L) takes about 10 hours. Recommendation 1.15.4, recommends a 'trough concentration' (the level of gentamicin in the baby's bloodstream shortly before a further dose is given) of less than 2 mg / L. This study would suggest that a neonate may have a higher than trough concentration gentamicin level for up to 10 hours following *in utero* exposure. However, as the study notes: serum concentrations of greater than 6 to 8 micrograms / ml (6 to 8 mg / L) are associated with greater clinical response, a figure consistent with recommendation 1.15.8. This recommends a minimum gentamicin peak concentration of 8 mg / L if Gram negative bacteria are suspected. The study would suggest that even an interval as short as 1 hour between gentamicin administration and birth, will result in gentamicin levels that are less than the therapeutic threshold recommended by the NICE guideline, but that further dosing of the neonate has the potential to significantly increase the concentration above gentamicin peak concentration. The study reports no difference in duration of neonatal antibiotic use and mean creatinine serum levels between groups. None of the neonates demonstrated compromised urinary outputs.

A narrative review (Viel-Theriault et al. 2019) about the transplacental passage of antibiotics and their impact on neonatal management was also checked for original studies. The paper includes a Cochrane review (Chapman et al. 2014) investigating antibiotic regimens for management of intra-amniotic infection. This focusses on different antibiotic treatment regimens for the mother but it does contain some limited indirect evidence of the prophylactic effect of intrapartum antibiotics on neonatal sepsis. It contains 1 study (n=116; very low quality evidence) that reports no effect on rates of neonatal sepsis of intrapartum clindamycin-gentamicin compared with intrapartum placebo (risk ratio [RR] 1.11, 95% confidence interval [CI] 0.23 to 5.27). The review also reports no significant differences were found in the rate of maternal bacteraemia or early neonatal sepsis for intrapartum versus immediate post-partum ampicillin/gentamicin treatment of the mother. However, for neonatal pneumonia or sepsis, intrapartum treatment was superior (1 trial, 45 neonates; RR 0.06, 95% CI 0.00 to 0.95; very low quality evidence).

Topic expert feedback

We sent questionnaires to 9 topic experts and received 3 responses from: a consultant medical microbiologist; a principal clinical pharmacist specialising in neonatology, paediatrics and women's health; and a senior lecturer in children's nursing with a special interest in paediatrics and infectious diseases.

We asked topic experts if they thought there was a gap in the NICE guideline about the management of neonates with early onset infection requiring antibiotics who have already been exposed to gentamicin *in utero*. One expert responded to say they did not think there was a gap. They commented that evidence suggests peak foetal levels are about one-third the concentration of maternal levels, and that this alone would not provide an adequate therapeutic dose. A maternal-foetal peak level ratio of one-third is reported by Locksmith et al. 2005 which reports peaks of 18.2 mg / L and 6.9 mg / L for mother and foetus, respectively based on 5.1 mg / kg every 24 hours dosing. The same topic expert expressed concern that there would not be time to check gentamicin levels before giving a first neonatal dose and that it would be difficult to know when to give the first dose. They also commented that for various reasons including selective resistance that use of cefotaxime as an alternative antibiotic was not an acceptable option.

One of the 2 respondents (a committee member for the NICE guideline) who thought there was a gap about this issue, noted it was discussed during guideline development and there was insufficient evidence to make recommendations. Despite acknowledging a gap, overall they felt the risk of ototoxicity and nephrotoxicity was outweighed by the need to treat neonatal sepsis in the first hour (recommendation 1.3.9). The expert commented that the risk of toxicity from intrapartum gentamicin exposure was low because: intravenous gentamicin doses given during labour peak at 30 minutes post-dose; that gentamicin is processed by pregnant women about 50% faster than non-pregnant women; and that gentamicin's half-life is 45% to 56% lower during pregnancy. They also noted that studies have shown peak foetal levels of gentamicin to be 34% to 42% of maternal levels. The same topic expert noted that babies born with high gentamicin levels was a 'very rare event', often the result of administrative error and identifiable by their impaired renal function.

We also asked topic experts for their opinions on adding the following wording to recommendation 1.4.1: 'If gentamicin has been given as an intrapartum antibiotic, check the trough blood gentamicin concentration. Take this into account before giving any further doses (see section 1.15 on therapeutic drug monitoring for babies receiving

gentamicin), but if there is an urgent need for gentamicin consider giving it before results are known.'

Two out of 3 topic experts did not think the proposed wording was acceptable. One topic expert reasserted that adding this wording to recommendation 1.4.1 would act to delay treatment and that it does not account for the potentially very variable interval between *in utero* gentamicin exposure and birth. A second expert agreed with checking gentamicin levels before giving the first neonatal dose but that this should be conditional and take account of the interval between intrapartum administration and birth, the dose, and whether baby presented with renal impairment. In the latter situation they noted it could be worth waiting for the gentamicin serum level if it can be processed quickly. However, they agreed with giving a first neonatal dose before gentamicin serum level is known when the treatment need is urgent, as waiting would risk sepsis treatment failure due to inadequate gentamicin levels. They advised in those situations it might be worth taking the gentamicin level 6 hours before any second dose. No reference is given for this timing, but it does concur with the gentamicin half-life estimated by Locksmith et al. (2005).

A second topic expert commented that the proposed wording poses a set of unanswered questions about what to do next after a practitioner receives the gentamicin serum concentration results. They commented that any recommendations about how to proceed would need to be based on the level of gentamicin serum concentration.

We also asked topic experts about their opinions on adding the following wording to recommendation 1.15.1: 'If gentamicin was given as an intrapartum antibiotic and trough levels are still high, treat the first neonatal dose as the second dose overall (also see recommendation 1.4.1 on investigations before starting antibiotics in babies who may have early onset infection).'

Two out of 3 topic experts did not think the proposed wording was acceptable. One commented that babies who need a second gentamicin dose are 'very sick.' They emphasised the risks of undertreatment in this group from insufficient gentamicin serum concentration posed by treating an intrapartum dose as a first dose. Another topic expert felt more clarification is needed and that a baseline level serum level (not a trough level) would need to be taken earlier before any second dose was given. They also commented that the wording does not make it clear how to proceed if the gentamicin level is 'high' and that the wording does not specify a threshold above which levels would be considered 'high.' They noted in practice that subsequent management of the baby would be guided by cultures, C-reactive protein levels and clinical status.

NICE internal clinical feedback

Clinical feedback received from within NICE also highlighted the risk posed to neonates in delaying antibiotic treatment by amending recommendations to include gentamicin serum concentration checks in neonates exposed to gentamicin *in utero.* However, it was also noted there was a potential issue with lack of recommendations, and that gentamicin does cross into the placenta but there is currently a lack of data to develop useful recommendations in this area. Additionally, NICE received information about an in process audit of cases of babies born with high gentamicin levels, intelligence which concurs with the original enquirer's concerns. We will track this audit and assess its impact on the NICE guideline when it reports.

Information considered in previous surveillance of this guideline

There have been no previous surveillance reviews for this NICE guideline.

Information considered when developing the guideline

Recommendation 1.4.1 and recommendations in section 1.15 about therapeutic drug monitoring in babies receiving gentamicin are primarily impacted by this enquiry. These recommendations date from 2012.

Recommendation 1.4.1 is based on 23 cohort studies of largely low to moderate quality about investigations in babies about to start antibiotic treatment. When making these recommendations the committee also considered existing recommendations in NICE's guidelines on meningitis (bacterial) and meningococcal septicaemia in under 16s, fever in under 5s, urinary tract infection in under 16s, postnatal care and NICE's full guideline on antibiotics for early-onset neonatal infection.

The committee considered a blood culture to be the reference standard for identification of bacterial infection and therefore recommended it before starting antibiotic treatment.

Recommendations in section 1.15 date from 2012 and are based on safety recommendations in the National Patient Safety Agency guidance from February 2010, 6 observational studies largely assessed as very low quality providing direct evidence, and a

further 6 studies investigating therapeutic drug monitoring as part of a package of care (NICE's full guideline on antibiotics for early-onset neonatal infection). The evidence reported a variety of approaches for monitoring and dosage adjustment, and no single study provided strong evidence to support a particular approach to monitoring. The committee noted that none of the study designs or approaches to pharmacokinetic monitoring was sufficiently alike to enable an evaluation of consistency in outcomes. None of the included studies addressed the issue of managing neonates who have been exposed to gentamicin *in utero*. The committee agreed that peak gentamicin concentrations need not be monitored routinely, but they should be monitored in carefully selected neonates. Commenting about 2 studies that used renal impairment as the basis for monitoring and adjustment of gentamicin dosage, the committee noted that creatinine is a late marker of renal damage due to gentamicin. It does not reflect the immediate effects of gentamicin toxicity and can be affected by other factors, including infection.

The committee noted the difficulty in specifying target peak and trough gentamicin concentrations in the absence of knowledge about the causative micro-organism of an early onset neonatal infection. The consensus view was that healthcare professionals should aim initially for a peak concentration of 8mg / L in neonates with a Gram negative or staphylococcal infection and should be measured within 1 hour of starting the gentamicin infusion. They agreed the target trough concentration for initial dosing should be less than 2 mg / L.

Conclusions

Evidence from 1 small RCT suggests gentamicin cord concentration peaks at about 6 mg to 7 mg / L up to 1 hour after administration and has a half-life of about 5 to 6 hours. This is based on a dosage for the mother very similar to that in recommendation 1.5.4. This could mean that a baby born 1 hour or less after administration of gentamicin to the mother could have a serum level of gentamicin approaching that in recommendation 1.15.8, a therapeutic level for Gram negative bacteria of 8 mg / L. *Inutero* exposure in this situation should offer some protection against neonatal sepsis reducing the need for further neonatal doses and hence the risk of accidental overdosing. Evidence for the prophylactic effect of *in utero* exposure to gentamicin seen during this surveillance review is mixed and indirect. A narrative review used to identify additional evidence for this exceptional review notes that the antibiotic threshold for foetal protection against early onset sepsis is not well defined (Viel-Theriault et al. 2019). This is consistent with the NICE guideline committee conclusions when making recommendations about intrapartum antibiotics for preventing early onset neonatal infection before birth. The committee noted that there

was no evidence identified on the effects on intrapartum antibiotics on the number of neonatal infections. However, they noted antibiotics reduce the number of maternal infections in pre-term labour and as infections such as chorioamnionitis are important risk factors for neonatal infection, intrapartum antibiotics are very likely to reduce the risk to the neonate (rationale on intrapartum antibiotics from the NICE guideline).

Although there is the possibility of overdose based on studies identified in this surveillance review, the actual prevalence of this rare event and whether it is increasing are currently anecdotal. A topic expert consulted during this review described this as a 'very rare event.' A committee member consulted during this surveillance noted a lack of evidence to make definitive recommendations about this issue, and this surveillance review has found only 1 RCT. Topic experts have raised concerns that any additional wording to check gentamicin serum levels could cause dangerous treatment delays and that the risk of delay outweighs the risk of overdose. They also noted recommendations would need to be more conditional to take account of the time interval between intrapartum administration and birth and the dosage, to avoid not only overdosing but also treatment failure resulting from sub-therapeutic neonatal gentamicin serum levels. Currently only 1 small RCT has been unidentified about gentamicin serum levels *in utero*, and it is insufficient on its own to base recommendations on.

Considering all these factors it is concluded that there is currently not enough evidence to amend recommendations about the use of gentamicin in neonates who have been exposed to it *in utero*. We will continue to monitor this area for emerging evidence. We will also track an audit of cases of neonates born with high gentamicin levels that we have been alerted to and assess its impact on the NICE guideline when it reports.

Equalities

No equalities issues were identified during the surveillance process.

Overall decision

We will not update recommendations about the use of gentamicin in neonates who have previously been exposed to gentamicin *in utero* at this time. We will track an ongoing audit of cases of babies born with high gentamicin levels and assess its impact on the NICE guideline when it reports.

ISBN: 978-1-4731-4751-5