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Are postnatal ampicillin levels actually related to the duration of intrapartum antibiotic prophylaxis prior to delivery? A pharmacokinetic study in 120 neonates

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ABSTRACT

Objective To assess ampicillin levels according to the duration of intrapartum antibiotic prophylaxis (IAP).

Design Prospective cohort single-centre study.

Setting Tertiary care centre (Modena, Italy).

Patients 120 neonates ≥ 35 weeks' gestation exposed to IAP.

Interventions Neonates were divided into four groups, according to the duration of IAP prior to delivery: group 1 (n=30; <1 hour), group 2 (n=30; ≥ 1 and <2 hours), group 3 (n=30; ≥ 2 and <4 hours) and group 4 (n=30; ≥ 2 doses, ≥ 4 hours).

Main outcome measures Blood samples were collected at delivery (from the umbilical cord) and at age 4 hours (from a peripheral vessel).

Results Median duration of IAP was 121 min (range 7–2045 min). Median ampicillin levels in umbilical cord blood were 10.4 $\mu\text{g/mL}$ (IQR 6.4–14.9) and in peripheral blood were 4.7 $\mu\text{g/mL}$ (IQR 2.8–6.4 $\mu\text{g/mL}$). Umbilical cord blood levels reached a peak approximately 30 min after IAP and then declined significantly ($p < 0.001$). Peripheral blood levels did not differ among study groups. Neonates exposed to a full loading dose (n=115) had peripheral blood levels 2.5–70 times higher than the minimal inhibitory concentration for group B streptococcus. There was no relationship between neonatal ampicillin concentrations and the duration of IAP prior to delivery ($\beta = -0.0003$, 95% CI -0.02 to 0.001 , $p = 0.680$).

Conclusions Ampicillin levels reach a peak in the umbilical cord blood within 30 min of intrapartum administration. After a full loading dose, bactericidal levels persist for at least 4 hours after birth and seem independent of the duration of IAP prior to delivery.

INTRODUCTION

Group B streptococcus (GBS) is a leading cause of early-onset sepsis (EOS, the disease presenting at age 0–6 days). Currently, the prevention of GBS-EOS relies on intrapartum antibiotic prophylaxis (IAP).¹ The actual mechanism of action is unknown. IAP might protect the neonate by achieving adequate levels in both fetal circulation and amniotic fluid, by decreasing the microbiological load of vaginal GBS or some combination thereof.

In order to maximise fetal exposure, US consensus guidelines^{2–4} recommend that intrapartum beta-lactam antibiotics (penicillin, ampicillin or cefazolin) be given at least 4 hours prior to delivery (adequate IAP). This threshold is not

What is already known on this topic?

- ▶ The optimal duration of intrapartum antibiotic prophylaxis (IAP) required to achieve bactericidal levels in fetal and neonatal circulation is uncertain.
- ▶ Previous studies have investigated maternal and/or fetal serum levels of beta-lactam.
- ▶ No studies evaluated the pharmacokinetic in the neonatal compartment or the persistence of effective neonatal concentrations over time.

What this study adds?

- ▶ Ampicillin levels reach a peak in the umbilical cord blood within 30 min of intrapartum administration.
- ▶ After a full loading dose, effective neonatal concentrations persist at least 4 hours and seem independent of the duration of antibiotics prior to delivery.
- ▶ These data could influence the clinical management of infants who receive 'inadequate' IAP and perhaps redefine 'adequate' IAP.

based on firm evidence⁵ and the optimal duration of IAP for preventing GBS-EOS remains uncertain.^{5–8} The study of GBS neonatal colonisation (a surrogate marker of infection) has provided conflicting results,^{5 8–11} with some studies reporting a significant reduction in neonatal colonisation after 2 hours¹⁰ or less than 1 hour of IAP.^{8 11} A number of studies have evaluated penicillin G or ampicillin concentrations in maternal and/or fetal serum.^{12–15} Levels of beta-lactam in umbilical cord blood increase to well over the minimum inhibitory concentration (MIC) for GBS after a few minutes of IAP. However, no studies have evaluated serum levels directly in neonatal blood after delivery. This information is essential to understanding how long effective levels will be maintained in the neonatal compartment as well as ampicillin pharmacokinetics.

The aim of this study was to determine whether ampicillin levels in the neonatal compartment after birth are significantly lower in neonates exposed to IAP for less than 4 hours prior to delivery compared with infants exposed to longer durations of IAP.



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MATERIALS AND METHODS

Study design

This is a prospective cohort study carried out at the Azienda Ospedaliero-Universitaria of Modena (Italy), a tertiary care centre that advocates a strategy of recto-vaginal culture screening at 35–37 weeks of gestation. The study includes neonates of mothers exposed to IAP for different durations (either less or more than 4 hours) prior to delivery, according to Centers for Disease Control and Prevention (CDC) guidelines.² A loading dose of intravenous ampicillin (2 g) is given during active labour and is followed by 1 g administered every 4 hours. The full administration of each dose is usually reached within 15 min. According to our local protocol, asymptomatic neonates ≥ 35 weeks of gestation exposed to inadequate IAP undergo serial physical examinations without any laboratory evaluation or empirical antibiotics.¹⁶ The study protocol was approved by the local ethical committee (Protocol no 159/13). A written informed consent was obtained from each participant. Patients were enrolled from May 2014 to February 2016. No neonates in study period had culture-proven GBS-EOS.

Exclusion criteria

Neonates were excluded if (1) they had < 35 weeks' gestation; (2) they were exposed to more than one intrapartum antibiotic; (3) they were given antibiotics other than ampicillin; (4) they were exposed to antibiotics in the postpartum period; (5) they had kidney failure or malformations and (6) they were born to a mother with a multiple gestation, hypertension or kidney disease.

Study groups

Ampicillin-exposed neonates were divided into four groups, according to the duration of IAP, starting from the beginning of the infusion: group 1 ($n=30$; IAP < 1 hour), group 2 ($n=30$; IAP ≥ 1 and < 2 hours), group 3 ($n=30$; IAP ≥ 2 and < 4 hours) and group 4 ($n=30$; IAP ≥ 2 doses and ≥ 4 hours). Blood samples were collected (1) at delivery, from the fetal side of the placenta after cord clamping (umbilical cord) and (2) at age 4 hours (from a neonatal peripheral vessel). This threshold was arbitrarily established in order to confirm the persistence of bactericidal levels after birth. We considered the neonatal ampicillin half-life (approximately 4 hours)¹⁷ and, as starting point, the interruption of maternal ampicillin supply at delivery.

Ampicillin assay

Blood samples were collected into serum test tubes and centrifuged at $3000 \times g$ for 10 min at 4°C . Serum was separated and samples were kept at -80°C until high performance liquid chromatography (HPLC) analysis. The HPLC method used is a modification of a published method (1–2).^{13 18} Ampicillin and penicillin G (Internal Standard, IS) for standard calibration and biological control samples were purchased from Sigma-Aldrich (St. Louis, Missouri, USA). Briefly, $350 \mu\text{L}$ of serum were spiked with $20 \mu\text{L}$ of IS solution ($400 \mu\text{g}/\text{mL}$) and vortexed. Samples were loaded onto a Strata SPE cartridge (Phenomenex, Bologna, Italy), which was preconditioned with acetonitrile (1 mL), followed by water (1 mL) and then eluted with acetonitrile (1 mL). The eluate was evaporated under nitrogen at 40°C . The residue was reconstituted in $200 \mu\text{L}$ of mobile phase. An aliquot of $50 \mu\text{L}$ was injected into the chromatographic system.

The liquid chromatographic instrument was a Beckman-Coulter System Gold model. The analytical column was a Kinetex C18 $150 \times 4.6 \text{ mm ID}$, $5 \mu\text{m}$ (Phenomenex) preceded by

a guard column of the same kind. The analysis was performed in gradient mode, with a mobile phase starting at 10% and linearly progressing to 68% acetonitrile in buffer $50 \text{ mM NaH}_2\text{PO}_4$ pH 2.4 flowing at $1 \text{ mL}/\text{min}$. The eluate was monitored at 219 nm, and the ratio of the area under the peaks (ampicillin/IS) was used for quantitation. Calibration standards for chromatographic analysis were prepared by addition of ampicillin to a donor serum in order to obtain analyte concentrations of $0\text{--}30 \mu\text{g}/\text{mL}$. The sensitivity of the analytical technique was expressed as the lower limit of quantification (LLOQ). The LLOQ of the method was $0.2 \mu\text{g}/\text{mL}$. Intraday and interday imprecision of our HPLC assay was tested by processing quality control (QC) samples during three consecutive sessions, five samples at three different concentrations, covering the whole calibration range (6, 10 and $25 \mu\text{g}/\text{mL}$, respectively). QC samples were prepared in-house on ampicillin-free serum samples spiked with ampicillin. Performance was evaluated using the variation coefficient expressed as a percentage (CV%) for each ampicillin control level. Calibration curves were linear over the ampicillin concentration range from 0 to $30 \mu\text{g}/\text{mL}$, with an average determination coefficient $r^2 = 0.98 \pm 0.01$. Intraday performance of the assay at 6, 10 and $20 \mu\text{g}/\text{mL}$ was 12.9%, 9.6% and 10.7%, while the interday performance was 13.2%, 14.7% and 10.7%, respectively. The average recovery ranged from $73.4 \pm 4.5\%$ to $78.4 \pm 5.8\%$ for low and medium ampicillin QC standards, respectively. The absence of interfering endogenous components at the retention time of ampicillin and penicillin G was demonstrated by the analysis of blank serum samples of the same matrices from six different sources. The threshold of susceptibility of GBS is $\leq 0.25 \mu\text{g}/\text{mL}$ for ampicillin.²

Statistical analyses

The sample size was calculated by assuming a mean difference of serum ampicillin concentrations of $0.25 \mu\text{g}/\text{mL}$ (SD 0.25) among neonatal groups (according to the duration of IAP prior to delivery). We also assumed a hypothetical 30% sample loss (missed cases, insufficient sampling or technical failures). On the basis of this estimate, a sample size of 30 patients in each cohort would be required to achieve 80% power (alpha level 5% using a two-sided test).

Data were expressed with mean and SD, median and IQR or number (percentage); categorical variables were compared using the χ^2 test. Continuous variables were compared among groups using the one-way analysis of variance and Bonferroni post hoc pairwise comparison test or Kruskal-Wallis test followed by the Dunn test for multiple pairwise post hoc comparisons, as appropriate. Ordinary least squares regression was used to assess the relationship of the neonatal serum ampicillin concentration with the cord blood concentration and duration of IAP prior to delivery. A plot of cord and neonatal serum ampicillin concentrations versus duration of IAP in minutes is reported with a linear regression fit of serum ampicillin levels at age 4 hours. All analyses were conducted using Stata/SE for Windows version 14.1 (College Station, Texas, USA). An α of 0.05 was considered significant.

RESULTS

Thirteen mothers refused consent to participate. Blood samples were collected from 142 neonates. Among them, 138 were healthy-appearing and 4 had mild respiratory symptoms with sterile cultures. Twenty-two of 142 (15.4%) were excluded because of insufficient sampling ($n=10$), technical failures ($n=3$) or missed cases ($n=9$).

Table 1 Demographics of maternal and neonatal populations in four study groups and duration of UIAP

	Group 1 (<1 hour)	Group 2 (≥ 1 and <2 hours)	Group 3 (≥ 2 and <4 hours)	Group 4 (≥ 4 hours)
Cases, n	30	30	30	30
Sex, M/F	18/12	9/21	17/13	19/11
Duration of IAP, min*	37.5 (23–46)	98.0 (79–109)	163.0 (145–191)	620.5 (420–958)
Gestational age, weeks*	39 (39–40)	39 (38–40)	40 (39–40)	40 (39–41)
Birth weight, g*	3455 (3135–3715)	3175 (2980–3730)	3385 (3180–3675)	3385 (3240–3620)
Maternal age, years*	34.5 (28–38)	31.0 (29–35)	31.5 (26–36)	32.0 (30–34)
Maternal BMI at delivery, median (IQR), kg/m ²	26.75 (24.24–29.41)	27.51 (24.34–29.41)	25.45 (24.22–29.75)	27.58 (24.91–31.11)
Ethnicity, n (%)				
Caucasian	19 (63)	21 (70)	20 (67)	17 (57)
African	10 (33)	4 (13)	9 (30)	9 (30)
Asian	1 (3)	5 (17)	1 (3)	3 (10)
South-American	0	0	0	1 (3)

*Values are expressed as median (25th to 75th percentiles).

BMI, body mass index; IAP, intrapartum antibiotic prophylaxis; F, female; M, male.

The remaining 120 neonates are the subject of the study. Two of 120 were <37 weeks of gestation.

The median duration of IAP prior to delivery was 121 min (IQR 59–241 min). In group 4, the median number of doses was 3 (range 2–9).

Demographics

Table 1 presents demographics of maternal and neonatal populations in the four study groups. There were no significant differences among them, except that group 4 had a slightly higher gestational age (clinically not influential) than group 2 ($p=0.042$).

Median ampicillin levels

The median level in umbilical cord blood samples from the 120 newborns was $10.4 \mu\text{g/mL}$ (IQR 6.4–14.9 $\mu\text{g/mL}$). At age 4 hours, the median peripheral blood level was $4.7 \mu\text{g/mL}$ (IQR 2.8–6.4 $\mu\text{g/mL}$).

Five of 120 newborns were born within 15 min after the beginning of maternal IAP. Because the infusion of each dose took place in approximately 15 min, ampicillin levels in these five neonates are provided separately. They had a median umbilical cord blood level of $14.3 \mu\text{g/mL}$ (range 5.7–26.1 $\mu\text{g/mL}$) and median peripheral blood level of $0.9 \mu\text{g/mL}$ (range 0.1–2.5 $\mu\text{g/mL}$). Only one neonate (exposed to IAP for 7 min

prior to delivery) had a peripheral blood level under the threshold of susceptibility of GBS to ampicillin ($\leq 0.25 \mu\text{g/mL}$).²

In the remaining 115 neonates (exposed to IAP >15 min prior to delivery), the median umbilical cord blood level was 10.3 (IQR 6.4–14.8) and the median peripheral blood level was 4.7 (IQR 3.1–6.6). No neonates had levels under the MIC for GBS.

Ampicillin levels according to study group

Table 2a details ampicillin levels of the 120 neonates in the four study groups. Cord blood levels were significantly different ($p<0.001$), with a progressive, significant decline from group 1 to 3. Peripheral blood levels (at age 4 hours) had no significant differences ($p=0.06$). Results were confirmed for both cord ($p<0.001$) and peripheral blood ($p=0.245$) when only the 115 neonates exposed to IAP for more than 15 min prior to delivery were analysed (table 2b).

Ampicillin levels in umbilical cord serum according to duration of IAP (minutes)

Figure 1 displays ampicillin concentrations in the 115 neonates exposed to more than 15 min of IAP prior to delivery. Concentrations rose rapidly and reached a peak approximately 30 min after administration of the loading dose of ampicillin. No further

Table 2 Comparison of ampicillin concentrations in umbilical cord and peripheral blood according to study groups:

(a) Analyses include all neonates					
Ampicillin concentration, median	Group 1 (<1 hour)	Group 2 (≥ 1 and <2 hours)	Group 3 (≥ 2 and <4 hours)	Group 4 (≥ 4 hours)	p*
Umbilical cord blood, $\mu\text{g/mL}$	16.36† (14.23–19.49)	11.92‡ (8.97–14.8)	7.72§ (5.33–11.07)	6.44 (4.87–7.92)	<0.001
Peripheral blood, at age 4 hours, $\mu\text{g/mL}$	4.21 (2.55–5.58)	5.52 (4.21–6.97)	4.96 (3.04–6.56)	4.29 (2.52–6.74)	0.06
(b) Analyses include 115 neonates exposed to IAP >15 min prior to delivery					
Ampicillin concentration, median	Group 1 (>15 min <1 hour)	Group 2 (≥ 1 and <2 hours)	Group 3 (≥ 2 and <4 hours)	Group 4 (≥ 4 hours)	p*
Umbilical cord blood, $\mu\text{g/mL}$	16.74† (14.57–19.49)	11.92‡ (8.97–14.8)	7.72§ (5.33–11.07)	6.44 (4.87–7.92)	<0.001
Peripheral blood, at age 4 hours, $\mu\text{g/mL}$	4.47 (3.59–5.60)	5.52 (4.21–6.97)	4.96 (3.04–6.56)	4.29 (2.52–6.74)	0.24

Values are expressed as median (25–75 percentiles).

*p value from Kruskal-Wallis test; $p<0.05$ adjusted for multiple comparisons.

†Group 1 versus groups 2, 3 and 4.

‡Group 2 versus groups 1, 3 and 4.

§Group 3 versus groups 1 and 2.

IAP, intrapartum antibiotic prophylaxis.

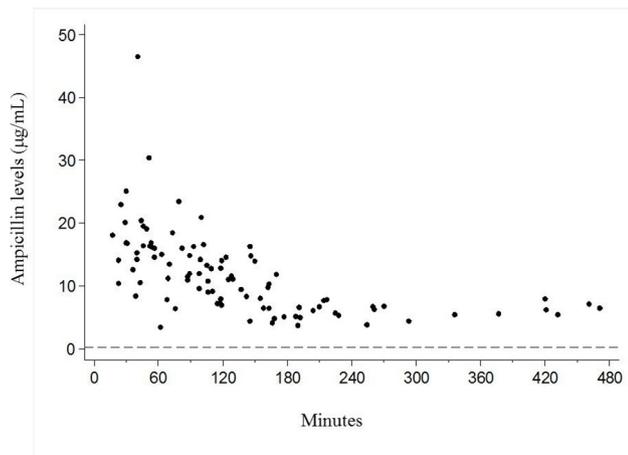


Figure 1 Ampicillin concentrations in umbilical cord serum samples are plotted according to the duration (in minutes) of intrapartum antibiotic prophylaxis (IAP) prior to delivery. For greater clarity, the figure includes only neonates exposed to up to 480 min of IAP. Data were calculated for patients receiving IAP for more than 15 min prior to delivery. The dotted line represents the threshold of susceptibility of group B streptococcus to ampicillin.

peaks were observed among the 30 neonates (group 4) exposed to at least two doses of IAP.

Ampicillin levels were from 10 to 185 times higher than the MIC for GBS.

Ampicillin levels in peripheral serum according to duration of IAP (minutes)

Figure 2 displays ampicillin concentrations at age 4 hours in the 115 neonates exposed to more than 15 min of IAP prior to delivery. The regression line showed no relationship between neonatal ampicillin concentrations and duration of IAP prior to delivery ($\beta = -0.0003$, 95% CI -0.02 to 0.001 , $p = 0.680$).

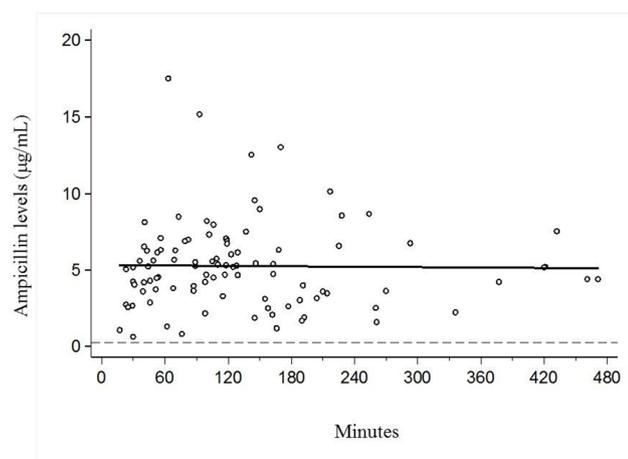


Figure 2 Ampicillin concentrations in serum samples from the peripheral vessel (at age 4 hours) are plotted according to the duration (in minutes) of intrapartum antibiotic prophylaxis (IAP) prior to delivery. For greater clarity, the figure includes only neonates exposed to up to 480 min of IAP. Data were calculated for patients receiving IAP for more than 15 min prior to delivery. The regression fit (solid line) describes the trend in distribution. The dotted line represents the threshold of susceptibility of group B streptococcus to ampicillin.

Neonates had ampicillin levels from 2.5 to 70 times higher than the MIC.

Regression analyses

The scatter plot and regression line of ampicillin concentrations (in the umbilical cord or peripheral blood at age 4 hours) versus maternal body mass index at delivery did not show any relationship, nor did birth weight or ampicillin levels at age 4 hours.

DISCUSSION

In order to define the minimum duration of IAP needed for effective prevention of EOS, this study evaluates both umbilical cord and peripheral neonatal blood ampicillin levels, according to the duration of IAP prior to delivery. This information is essential. Indeed, due to the rapidity of their labour, as many as 50% of women in some studies are unable to meet the recommended 4-hour duration.^{5 19} In order to optimise fetal exposure, some authors therefore suggest modifying labour strategies, by 'labouring down' or delaying pushing or avoiding artificial rupture of membranes until the required 4 hours have elapsed.^{20 21} The duration of IAP also affects the management of well-appearing neonates; indeed, some guidelines recommend laboratory evaluation for neonates with prolonged membrane rupture or preterm delivery.² Defining the duration of IAP necessary to prevent GBS-EOS is, therefore, important in order to minimise unnecessary evaluation and overtreatments²² among mothers and neonates. Two retrospective observational studies have provided evidence that at least 4-hour duration of IAP is associated with a lower risk of GBS-EOS.^{23 24} However, these studies are complicated by a number of possible bias and pitfalls. Indeed, cases of GBS asymptomatic bacteraemia may be confirmed only in neonates evaluated²⁵ and the 2002 CDC guidelines³ recommended evaluation only for neonates exposed to IAP less than 4 hours prior to delivery. Consequently, GBS may have been confirmed only in neonates exposed to short durations. Furthermore, advanced intrauterine infection may lead to failure to progress or fetal distress resulting in an emergency caesarean section.^{26 27} Neonates frequently have a low Apgar score and are ill at birth.^{26 27} In these cases, IAP may not reach the 4-hour duration because of the emergency caesarean section, and it seems 'ineffective' (because of advanced intrauterine infection) rather than 'inadequate'.

Previous studies have investigated maternal and/or fetal serum levels of beta-lactam.¹²⁻¹⁵ Bloom and coworkers found that ampicillin levels far greater than the MIC for GBS were achieved within 3 min in all maternal and umbilical cord blood samples.¹² Barber and coworkers demonstrated that fetuses exposed to less than 1 hour of IAP prior to delivery had penicillin G levels significantly greater than all the other groups of patients exposed to more than 2 hours of IAP prior to delivery. Penicillin levels were 10-fold to 179-fold above the MIC for GBS in all fetal samples.¹⁴

The penicillin pharmacokinetic data can be extrapolated to estimate the concentration time profiles of ampicillin that is physicochemically very similar. Our results are comparable with Barbers' data. Ampicillin levels in umbilical cord blood at delivery reached a peak approximately 30 min after administration of the loading dose. Subsequent doses did not result in further peaks. Most importantly, at age 4 hours ampicillin levels in the peripheral blood of neonates exposed to a full loading dose (at least 16 min prior to delivery) were 2.5–70 times higher than the MIC. Levels were independent of the duration of IAP prior to delivery.

Overall, these results are consistent on what we have previously found.^{8–11} Rates of neonatal colonisation did not differ among neonates exposed to IAP for less than 1 to 12 hours prior to delivery.¹¹ However, the interpretation of current data requires some caution. Ampicillin levels above the MIC may be ineffective if the fetus has already become septic before exposure to IAP, and IAP failures may sometimes unevenly occur.^{28–29} Furthermore, antibiotics could sometime make a blood culture negative, without curing the EOS, complicating the assessment of the efficacy of treatment. Although concentrations well above the MIC are reached soon after the loading dose, neonates at risk for EOS still require observation after birth.³⁰

In conclusion, ampicillin levels reach a peak in umbilical cord blood within 30 min after IAP administration. Furthermore, after the full loading dose has been given, levels well over the MIC for GBS persist for at least 4 hours after birth and seem independent of the duration of IAP prior to delivery.

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Contributor All authors made substantive intellectual contributions to the published study and approved the final manuscript as submitted. AB and ZP designed the study and drafted the initial manuscript. MLBR and DG carried out the initial analyses, reviewed and revised the manuscript. KR and VB designed the data collection instrument, coordinated and supervised data collection and critically reviewed the manuscript. FFa and FFe conceptualised and designed the study, reviewed and revised the manuscript.

Contributors None.

Competing interests None declared.

Ethics approval The study protocol was approved by the ethical committee of the Azienda Ospedaliero-Universitaria di Modena (Italy) on 8 November 2013 (Protocol no 159/13).

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