The present overview is aimed at reporting the standard primary investigations that are mandatory in preterm and term newborns at admission to neonatal unit in the first hours after birth. Herein, the main neonatal screening tests for early detection of metabolic diseases are described as well as laboratory standard procedures (glycaemia, bilirubin, blood gas, infectious diseases analyses) monitoring parameters (vital signs recordings, blood and transcutaneous gas assessment, blood pressure recordings) and ultrasound pattern (cranial and cardiac).

Keywords: prematurity, screening, term newborn

Abbreviations: CRP, C reactive protein; HRSA, Human Resources Services Administration; MS/MS, tandem mass spectrometry; PKU, Phenylketonuria; TC, Transcutaneous

Term newborn – primary investigation

The concept of screening newborns, started in 1960, was primarily directed at early identification of disorders in which the clinical complications appeared in the postnatal period. Metabolic/genetic screening program should be performed on every newborn according each country policy [1].

Metabolic screening

Metabolic diseases result from biochemical abnormalities appearing after birth, when the infant is no longer protected by fetal-maternal exchange [2]. Phenylketonuria (PKU) was the first metabolic disorder known to benefit from early diagnosis and immediate dietary treatment [3,4]. There is evidence that infants complicated by PKU showed a normal development while receiving treatment [5]. The success on PKU screening was followed by the introduction in clinical practice of additional tests for metabolic diseases such as galactosemia, maple syrup disease and homocystinuria [6]. Of note, these tests are now applied to the same blood specimen obtained for PKU screening. From 1990 to date, tandem mass spectrometry (MS/MS) use in daily practice allowed the detection of more than 30 biochemical genetic disorders with a single assay at high specificity and at extremely low rate of false positive results [7,8]. Currently, the disorders detected by most MS/MS newborn screening program can be divided into three major categories: amino-acid disorders (including urea cycle defects), organic acid disorders and fatty acid oxidation defects [7].

In 1999, the American Academy of Pediatrics Newborn Screening Task Force recommended that Human Resources and Services Administration (HRSA), developed and implemented nationally recognized newborn screening system standards and policies [9] in collaboration with the Maternal and Child Health Bureau of HRSA and the American College of Medical Genetics. The following criteria were considered: (i) availability of an effective and rapid screening test and (ii) an efficacious treatment and adequate understanding of the natural history. Scientific committee identified 29 conditions appropriate for newborn screening and proposed a number of recommendations to move newborn screening programs towards uniformity (Table I).

Sampling modalities and storing are now standardized in each country [10]. To allow adequate dietary challenge for the newborn, sample should be collected after at least 24 h of oral feeding and before discharge from the hospital, generally by less than 5 days of age. If the newborn is discharged before 24 h, to avoid the risk of no sample at all, a filter paper sample should be collected before discharge and then repeated when the infant returns for routine check-up at about 1 week of age.

Infections of the neonate – primary investigations

Perinatal infections are important cause of postnatal morbidity and mortality. As many as 2% of fetuses are infected in utero, and up to 10% of infants may have infections in the 1st month of life. Maternal infection is often un-diagnosed during pregnancy as mother may be either asymptomatic or can have non-specific signs/symptoms at the time that acute infection occurs.

In the last decade, several studies have demonstrated the importance of maternal and neonatal risk factors of development of neonatal sepsis (Table II). Several laboratory tests have been evaluated for their ability to predict which of at risk infants can develop symptomatic or culture-proven sepsis, but, at this stage, no adequate sensitivity/specificty for a single test has been reported [2]. On the basis of these findings, investigators proposed different combinations of laboratory tests to enhance the early detection of infected neonates. However, results showed that the predictive value of combined laboratory test did not differ from individual test. Conversely, their accuracy was more predictive for negative cases [11]. For example, WBC differential count, immature-to-total neutrophil (I:T ratio) and C reactive protein (CRP) [12], although sensitivity/specificty is limited, total WBCs count and differential and I:T ratio can hypothesize bacterial infection. In this regard, CRP demonstrates high sensitivity and negative predictive value, especially when serial CRP determinations at birth and at 12 h are performed [11,13].

In case of an asymptomatic term-infant with positive laboratory tests, blood culture assessment and antibiotic therapy are recommended strategies up to culture results are negative.

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### Table I. Newborn screening panel recommended by American College of Medical Genetics expert panel [10].

<table>
<thead>
<tr>
<th>Organic acids</th>
<th>Fatty acid oxidation</th>
<th>Amino acid cycle</th>
<th>Disorders detected by other methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isovaleric academia</td>
<td>Medium chain acyl-CoA dehydrogenase</td>
<td>Phenylketonuria</td>
<td>Hb SS-Sickle cell anemia</td>
</tr>
<tr>
<td>Glutaric aciduria</td>
<td>Very long chain acyl-CoA dehydrogenase</td>
<td>Maple syrup urine disease</td>
<td>Hb Sβ-thalassemia</td>
</tr>
<tr>
<td>3-Hydroxy-3-methylglutaric aciduria</td>
<td>Long chain 3-hydroxacyl-CoA dehydrogenase</td>
<td>Homocystinuria</td>
<td>Hb S/C disease</td>
</tr>
<tr>
<td>Multiple carboxylase deficiency</td>
<td>Trifunctional protein deficiency</td>
<td>Citrullinemia</td>
<td>Congenital adrenal hyperplasia</td>
</tr>
<tr>
<td>Methylenal academia due to mutase deficiency</td>
<td>Carnitine uptake defect</td>
<td>Argininosuccinic aciduria</td>
<td>Galactosemia due to GALT deficiency</td>
</tr>
<tr>
<td>3-Methylcrotonyl CoA carboxylase deficiency</td>
<td></td>
<td>Tyrosinemia type 1</td>
<td>Congenital hearing loss</td>
</tr>
<tr>
<td>Methylenal academia due to cobalamin A and B defects</td>
<td></td>
<td></td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>Propionic academia</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>3-Ketoliatholase</td>
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</tr>
</tbody>
</table>

GALT, galactose-1-phosphate uridylytransferase, gut-associated lymphoid tissue.

### Table II. Perinatal sepsis risk factors [19,26].

<table>
<thead>
<tr>
<th>Maternal and obstetric factors</th>
<th>Neonatal factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal peripartum fever</td>
<td>Prematurity and low birth weight</td>
</tr>
<tr>
<td>Premature or prolonged (&gt;18 h) rupture of membranes</td>
<td>Resuscitation at birth</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td></td>
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<tr>
<td>Vaginal colonization with GBS</td>
<td></td>
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<tr>
<td>Perineal colonization <em>Escherichia coli</em></td>
<td></td>
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<tr>
<td>Previous delivery of a neonate with GBS disease</td>
<td></td>
</tr>
<tr>
<td>Amniotic fluid problems (meconium-stained or foul-smelling, cloudy amniotic fluid)</td>
<td></td>
</tr>
<tr>
<td>Multiple gestation</td>
<td></td>
</tr>
<tr>
<td>Race (sepsis is more common in black than in white infants)</td>
<td></td>
</tr>
<tr>
<td>Sex (males are four times more affected than females)</td>
<td></td>
</tr>
<tr>
<td>Low socioeconomic status</td>
<td></td>
</tr>
<tr>
<td>Neonatal factors</td>
<td></td>
</tr>
<tr>
<td>Prematurity and low birth weight</td>
<td></td>
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<tr>
<td>Resuscitation at birth</td>
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</table>

GBS, group B streptococcus, Guillain-Barre syndrome.

### Preterm newborn – primary investigations

Preterm birth affects more than 500,000 babies in the United States each year [14]. In Italy, the incidence of preterm birth is 6.7% <37 week of gestation, 5.2% between 32 and 36 week of gestation and 0.9% <32 week [15]. Preterm birth is one of the leading causes of infant mortality and the leading cause of infant morbidity [16]. It accounts for >70% of neonatal deaths and almost half of long-term neurological disabilities [17]. Research indicates that preterm birth is a multifactorial disease caused by genetic, social and environmental factors, which most likely interact to increase risk [18,19].

### Neonatal care

Despite modern neonatal care, intensive care involves sophisticated measurement of temperature, respiration, cardiac function and oxygenation, and brain activity, clinical evaluation and preterm stabilization are the main steps for an accurate and successful management.

### Temperature determination

In order to avoid hypo/hyperthermia side effects, temperature assessment is suggested as often as every 30 min until thermo stability is achieved. After that, temperatures should be recorded every 1–3 h in preterm infants and every 4 h in the healthy term infant. Servo-controlled skin temperature is recommended.

### Cardiorespiratory monitoring

Newborn cardiac, respiratory, oxygenation status can be longitudinally recorded at 1-min interval by dedicated devices. Recordings are displayed on a visual screen. Oxygen saturation monitor relies on adequate perfusion to the site and the ability to detect arterial pulsation [20,21].

### Blood pressure

Blood pressure monitoring represents one of the main standard procedure to be performed in high-risk newborn when admitted to NICU. Changes in blood pressure, especially in first hours after birth may represent the warning sign of the risky complications occurring in high-risk newborn: hypotension, hypoxia reperfusion injury infections. Blood pressure is weight- and gestational age-dependent. It is measured by invasive and non-invasive methods.

### Transcutaneous blood gas monitoring

Transcutaneous measurement of oxygen and carbon dioxide tension is a non-invasive method that has recently offered some promise. Several studies have shown a good correlation between tc and arterial values [22].

### Blood glucose monitoring

Preterm and term newborn are at risk for disturbances in glucose homeostasis. Glycaemia assessment has to be determined soon after birth. The determination can be performed by laboratory enzymatic methods, such as the glucose oxidase or hexokinase method, but even bedside reagent test strip glucose analyzers (i.e. glucometers) can be used. A number of current references use 40–45 mg/dl as the lower limit of "normal" plasma glucose concentrations in the first 72 h of life [23].
Bilirubin monitoring
Both in preterm and term newborn, bilirubinemia assessment in the first hours after birth is required in order to avoid hyperbilirubinemia side effects. Bilirubinemia can be assessed by standard analyzers or by transcutaneous method.

Cranial and cardiac ultrasound
Cranial and cardiac ultrasound recordings are required especially in preterm newborn within the first 24 h from birth. Longitudinal monitoring is mandatory when some typical complications such as patent ductus arteriosus, brain immaturity are suspected.

Blood gas monitoring
Preterm infants are vulnerable to alterations in arterial oxygen or carbon dioxide tension that can contribute to the development of main prematurity complications [24]. Blood gas monitoring is mandatory in respiratory monitoring, especially when invasive procedures are performed (mechanical ventilation, nitric oxide supplementation etc.) [25].

Declaration of interest: The authors report no conflicts of interest.

References
9. Available at: http://www.mchb.hrsa.gov/screening