Hyperammonemias: differential diagnosis and impact of newborn screening on diagnosis
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Hyperammonemia is generally defined as ammonia of > 100 µmoles/L in neonates or >50 µmoles/L postnatally. The signs and symptoms of hyperammonemia include lethargy, seizures, coma, ataxia, irritability, sleep disorders, loss of appetite, vomiting, protein intolerance and visual hallucinations. Hyperammonemia may be due to inherited or acquired defects. Common causes, along with the degree of hyperammonemia, are listed below.

- Urea cycle enzyme deficiencies (↑↑↑↑)
- Transport defects of dibasic amino acids (↑↑↑)
- Some Organic acidurias (↑↑)
- Fatty acids oxidation disorders (↑↑)
- Urease containing micro-organism (↑)
- Liver disease (↑) - (↑↑)
- Defects in portal circulations (↑↑)

The most common and severe causes of hyperammonia are due to urea cycle defects (Figure 1)

As the treatment varies depending on the defect, differential diagnosis of hyperammonemia is important. Figure 2 shows the work-up of hyperammonemia.

In 2005 the Missouri State Department of Health expand newborn screening to include several urea cycle defects: argininosuccinate synthase deficiency (citrullinemia), and argininosuccinate lyase deficiency. The screening will not detect arginase deficiency, carbamyl phosphate synthase deficiency; hyperammonemia, hyperornithinemia, and homocitrullinemia (HHH) syndrome; N-acetylglutamate synthase deficiency, ornithine transcarbamylase (OTC) deficiency and arginase deficiency. Some of these disorders may be added in the newborn screening in the future.

The treatments include low protein diet, benzoate, sodium phenylacetate, supplementation with citrulline and arginine depending on the urea cycle defect, hemodialysis and peritoneal dialysis, and liver transplant.

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**Figure 1.**

**Figure 2.**
Pertussis is caused by *B. pertussis*, a gram negative bacterium. Infection caused by *B. pertussis* results in mild upper respiratory symptoms that progress to cough which progresses to paroxysms of cough. Pertussis is primarily a childhood disease with the highest incidence in children under 5 years of age. Milder and missed atypical cases occur in all age groups. Recent reports from the Centers for Disease Control, Missouri State Health Department and our own hospital data indicate pertussis infections are on the rise. The 5 year median number of cases in our northwestern health region was 32 cases while in 2003 season it rose to 146 cases. As of October this year 251 cases have been recorded in Missouri. Middle and High school associated pertussis outbreaks are being recognized increasingly. Neither disease nor vaccine provide life long immunity and vaccinated persons are at risk for infection 5-10 years post infection. Waning immunity to vaccination may be one of the reasons for increase in infection rate. CDC recommends health-care providers to consider pertussis in persons of any age with acute cough illness characterized by prolonged cough.

Several tests are available for diagnosis of pertussis; they include culture, direct fluorescent antibody (DFA) test, serology and polymerase chain reaction (PCR), nucleic acid amplification technique. Culture has been the traditional gold-standard assay; however the sensitivity of culture detection is influenced by several factors including the stage of disease, specimen collection and use of proper transport and culture media. Culture can take up to 3-7 days or more for detection. DFA test can be done rapidly within several hours but suffers from poor sensitivity and may produce cross-reactivity with normal oropharyngeal and nasopharyngeal flora. Serologies are useful in epidemiological studies and in acellular pertussis vaccine trials but are not yet available for routine clinical use. PCR is a highly sensitive methodology and can usually be completed with in 1-2 days. Previous reports have indicated PCR can be 2-3 fold more sensitive than culture or DFA.

Nasopharyngeal aspirates or nasopharyngeal swabs are the specimen of choice for bacterial culture, DFA test and PCR. Swabs for PCR should use Dacron (not cotton) inserted slowly through the nostril to the posterior pharynx and left for 10 seconds before withdrawing.

The CMH microbiology laboratory is developing a real-time PCR that is able to detect and differentiate *B. pertussis* and *B. parapertussis*, the causative agent of parapertussis. Previous PCR assays have used several *B. pertussis* targets including insertion sequences (IS), repeat elements, pertussis toxin promoter gene, adenylate cyclase gene and the porin gene. The PCR assay developed at CMH targets the insertion sequences present in multi-copy numbers (50-100 copies per cell) in the bacteria. While the presence of *B. pertussis* and *B. parapertussis* DNA in nasopharyngeal specimen strongly suggest active infection, as with any other laboratory test the result should be interpreted in conjunction with clinical presentation, patient history and other diagnostic tests.

Happy Holidays