This month's issue features milk allergies in children and choline in milk.

**Cheese Fights Antibiotic Resistance in Urinary Tract Infections**

- A Dutch study of urinary tract infections has found that eating cheese is associated with protection against the most common forms of *Escherichia coli* antibiotic resistance.
- The more cheese the participants in the study reported consuming, the lower their odds of getting a resistant urinary tract infection.
- Those whose diets featured plenty of chicken or pork had a higher probability of their urinary tract infections showing resistance to important antibiotics.

The Ommoord district of the city of Rotterdam, in the Netherlands, is known for its many residential towers. Among epidemiologists, it has a new notoriety. Between 2000 and 2016, researchers tested the urinary tract infections (UTIs) of Ommoord residents for resistance to a number of antibiotic drugs. The aim was to figure out why some people struggle with drug-resistant UTIs, but other people who catch UTIs get infected with bacteria that modern medicine has no trouble conquering. The Ommoord study has a simple conclusion [1]. At least in the Netherlands, eating chicken and pork is associated with an increase in the odds of having drug-resistant UTIs, but eating cheese reduces this. Cheese, in this sense, appears to promote a urinary tract that can be more easily soothed.

The antibiotic resistance data were recorded through routine medical procedures in Ommoord. There were many residents with urinary infections in the city over the study period whose diagnoses were carried out at the same laboratory. Every time this lab identified *Escherichia coli* in a urinary culture, its technicians performed a series of tests to see which of a list of antibiotics could kill the *E. coli* cells. Of these, 612 people completed dietary surveys, so Marlies Mulder, Bruno Stricker and their team of researchers could assess how much of several food groups the Ommoord’s UTI sufferers were consuming on a regular basis. The research team then modeled the data, such that one at a time, resistance to each antibiotic was predicted using the dietary data, while statistically removing the influence of additional factors that often correlate with diet (such as age, sex, and socioeconomic status).

Intriguingly, resistance to certain kinds of antibiotic drugs was linked to eating certain kinds of food. The odds of having a UTI resistant to cefotaxime was highest for people who ate a lot of chicken. Cefotaxime, like amoxicillin, is on the World Health Organization’s Model List of Essential Medicines. Those who consumed a lot of pork had a particularly high probability of their UTI demonstrating resistance to norfloxacin. However, a diet rich in pasteurized cheese cut the likelihood of a UTI with resistance to the most common type in the study—resistance to the drug, amoxicillin, which was found in 40% of the Ommoord UTIs. Cheese consumption also reduced resistance to amoxicillin-clavulanic acid. The more cheese that participants reported eating regularly, the lower their odds of antibiotic-resistant UTIs.

What might explain these patterns? To the researchers, the worrying finding for individuals with high chicken intake was no surprise at all. A few years ago, another study revealed that 94% of chicken that was on sale in retail outlets in the Netherlands contained *E. coli* with genes known as “ESBL genes” [2]. These genes produce extended-spectrum beta-lactamases—enzymes that fight antibiotics. Sequencing of ESBL genes has also revealed that those exact sequences found in bacteria from broiler chickens are genetically indistinguishable from sequences in human cultures—demonstrating the causal link [3]. Similarly, the association between pork consumption and norfloxacin resistance is most likely explained by the liberal use of antibiotics on pig farms.

Why cheese might lower the odds of amoxicillin-resistant UTIs is harder to state with confidence. A plausible answer put forward in the literature is that eating cheese helps to cultivate generally healthy gut microbiota, which in turn may make it hard for antibiotic-resistant bacteria to latch on and grow in the
body. The specifics of this mechanism—known as the “resistome” hypothesis [4]—are lacking, however. Even so, one small study that prescribed eating cheese alongside a dose of the antibiotic amoxicillin-clavulanic acid found that cheese consumption lowered amoxicillin-resistance rates found in enterococci bacteria (though not E. coli) [5].

So there seems to be some causal connection, but researchers have their work cut out to pin down exactly how cheese lowers UTI antibiotic-resistance rates. In the meantime, the dietary advice is clear for people who have struggled over the years with this potentially excruciating medical problem. If you want to keep eating chicken and pork, try to source it carefully from a farm that is sparing its use of antibiotics. Safer still, fill your shopping basket with cheese.


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Choline in Human Milk Plays a Crucial Role in Infant Memory

- **Choline** is an important nutrient present in human milk, and it plays a crucial role in fetal and infant development.
- **Choline** plays a particularly important role in brain development, and researchers have shown that it can influence infant memory.
- **Choline’s effects on memory** appear to occur as a synergistic effect with two other important nutrients, docosahexaenoic acid (DHA) and lutein.

Choline is an important vitamin-like nutrient that was officially recognized as an essential nutrient in 1998 [1]. It is an important structural component of our cells, as it is part of molecules called phospholipids that are abundant in our cell membranes. It is also important for the synthesis of the neurotransmitter acetylcholine, which is involved in memory and muscle control. Choline deficiency is thought to contribute to liver disease, atherosclerosis, and neurological disorders [2].

Choline is present in human milk, and is especially important for fetal and infant development [2,3]. “The hint that choline is important for infant development comes from the fact that in human milk, the supply of choline remains constant across the first year of life,” says Professor Carol Cheatham from the University of North Carolina at Chapel Hill. Other important nutrients, such as docosahexaenoic acid (DHA), are present in large quantities initially, but often level off after a few months.

Choline is known to play a key role in brain development. “Choline is important for synapse formation, it’s important for making cellular membranes, it’s important as a methyl donor, it’s important in the manufacture of acetylcholine, which is a neurotransmitter that is used in memory and other things, so it’s very important in the brain,” says Cheatham.

Given its importance in development, studies have suggested that pregnant and lactating women should ensure they consume adequate choline in their diet [3]. “It has been shown that eating choline will increase the choline in the breast milk,” says Cheatham. The richest food sources for choline are of animal origin, including milk, meat, and especially eggs.

Prenatal vitamin supplements do not contain sufficient choline, and studies have suggested that about a quarter of women in high-income countries and most women in low-income countries consume too little choline in their diet [3]. “We know that pregnant women in America are not consuming enough choline, so we need to increase that a bit,” says Cheatham. Having too little choline can have dire consequences. Women in the United States with diets lower in choline content are at significantly greater risk for having a baby with a neural tube defect or an orofacial cleft than women with diets higher in choline content [4,5].
Formulas derived from non-animal sources, particularly soy, have lower total choline concentrations than human milk, and the US Food and Drug Administration (FDA) requires that infant formula not made from cow’s milk be supplemented with choline [6]. “There is choline in most infant formulas now,” says Cheatham. Most formulas also contain two other nutrients that work with choline, DHA and lutein. “They have the big three in there now,” she says.

That’s a good thing, because choline may be crucial for infant brain development, and may work in conjunction with DHA and lutein. Cheatham found that choline played a particularly important role in memory, and acted in synergy with DHA and lutein [7]. “I think our study showed really good evidence that choline is very important to the brain, either by having its own action or because it assists the actions of other nutrients,” says Cheatham.

Previous studies in animals found that choline had some effects on cognition, but the results in humans have been mixed. There were some studies in adults that reported better cognitive function in those that ate diets higher in choline, but how choline might influence cognition in children was still unclear [8].

Cheatham wondered if the inconclusive findings of different nutrient studies might be because a lot of them looked at nutrients individually, rather than in combination with other nutrients. “I started getting interested in synergy between nutrients because I’ve been looking for potential reasons why we find effects in some studies but not in others,” she says.

Cheatham became interested in the synergistic effects between choline, DHA, and lutein due to the fact that they often appear together in nature, such as in eggs and in human milk. “These are always seen together, so you know that they must be working together,” she says.

Previous research indicated that these three nutrients might act in synergy [9,10]. DHA is known to work in concert with choline and other nutrients to improve synapse formation and cognition [11,12]. Some studies also suggested that DHA and lutein are independently associated with cognition [4,9,13-15]. “The three of them together are like the secret sauce of brains,” says Cheatham.

Cheatham and her colleagues decided to assess the influence of human milk choline, DHA, and lutein on the recognition memory abilities of six-month-old infants. They first analyzed human milk samples obtained three to four months postpartum for fatty acids, lutein, and choline. Then, at six months they invited participants to an electrophysiology session to test the infants’ recognition memory.

“Oh obviously a six-month-old can't tell you what he or she remembers,” says Cheatham. Instead, the researchers used scalp electrodes to record the electrical activity of the infants while they watched a computer screen. “We record that electrical activity, but we time lock it to an event that's happening on the computer screen in front of the baby,” she says. “So, they're just sitting on their mom's lap in front of the computer, passively watching pictures, and we get really good wave forms that are related to whether or not the infant brain is processing the information in front of them or not,” says Cheatham.

The researchers showed the babies one picture 12 times to familiarize them with it, before showing them 100 pictures. “Seventy of them will be the familiar picture and 30 of them will be brand new things that they're seeing one time each,” she says.

Of course, it’s hard to keep a 6-month-old’s attention, so the researchers only analyzed data from when a baby was actually looking at a picture on the computer. “So, we will get down to about 20 pictures in each condition, and we’ll come up with a grand average of the brain activity when the baby was seeing a familiar thing on the screen and the brain activity when the baby was seeing a novel thing on the screen,” says Cheatham. From the difference between these two brain activities, the researchers can infer recognition memory.

“We get really nice wave forms that will show that if it's a familiar picture, no processing is necessary, but if it's a novel picture, you get this really nice deflection in the data that shows processing,” says Cheatham. “We can use this to estimate the speed of processing, how well information is flowing across the synapse from neuron to neuron,” she says.

Cheatham and her colleagues then looked for evidence of synergy between the nutrients. “We wanted to find out if there is a model where DHA doesn't have an effect, choline doesn't have an effect, but when you put them together in an interaction, there is an effect,” says Cheatham. “It turns out we see that often,” she says.
The researchers found that higher choline levels with higher lutein levels were related to better recognition memory. “So, lutein was working with choline to improve speed of processing in the infant brain,” says Cheatham. Similarly, DHA and choline appeared to work together, with high choline and high DHA associated with better recognition memory.

Cheatham is planning larger follow-up studies to look at choline and its synergistic interactions in more detail. “In order to prove the synergy, you have to prove that both nutrients together are better than the single nutrients,” she says. “So, the study design would be to supplement some moms with DHA, some moms with choline, and some moms with both DHA and choline,” says Cheatham. These follow-up studies could also collect information on maternal diet, and could look at the three-way interactions among choline, DHA, and lutein.

Cheatham and her colleagues conclude that choline, in synergy with lutein and DHA, plays an important role in infant cognition and memory. But there’s a lot left to learn about the role of human milk choline in infant development. “Rest assured that the work is continuing,” she says.


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Ironing Out Allergy to Cow’s Milk Protein

- The recommended earliest age for the introduction of liquid cow’s milk to infants is generally set at 12 months (9 months in Canada).
- Formula or breast milk should not be replaced with cow’s milk before infants are 12 months of age to ensure they get sufficient iron in their diet.
- A recent investigation of over 2,000 children reports that delaying the introduction of cow’s milk to infants beyond 12 months of age is associated with an increased risk of allergy to cow’s milk.
- The current recommendation may need a modification to allow infants 6–12 months old to be exposed to small quantities of liquid cow’s milk to minimize their risk of developing cow’s milk allergy.
After hundreds of thousands of years of evolution and carrying the unrelenting burden of *survival of the fittest*, humans have increasingly become allergic to food [1-4]. Who would have thought? It seems like the ultimate contradiction of our time. Heading the list of serial offenders are nuts, seafood, eggs, wheat, soy, and cow’s milk [5-7]. About 8% of children and 5% of adults in Western countries are diagnosed with food allergies [8]. Scientists agree that the priming of allergic responses (sensitization) to some foods and the development of normal tolerance to foods generally occurs early in life [1, 6, 9]. Over the last two decades, the health authorities’ recommendations for when to introduce some of these foods to infants have radically changed as clinical investigators reveal new information that directly conflicts with past practices. One area of some confusion relates to the reason for the recommended late introduction of liquid cow’s milk to infants.

**What Is Food Allergy?**

Immune cells in the body are always on high alert so they can rapidly foil any attempted invasion by bacteria, viruses, and fungi. However, these cellular sentries can be a little trigger happy. Sometimes they open fire with their full chemical arsenal when they mistake, at the molecular level, a food component for a microbial invader. The cost of this error in judgement is tissue irritation and damage that then causes the symptoms typical of allergies. The history of human evolution has impersonally judged that, overall, there is more benefit from maintaining a highly vigilant immune system that protects the body from the threat of microbial diseases than the biological cost of allergic reactions in some individuals. An allergy is a hypersensitive immune response to a substance that is normally not harmful to most people. The inflammation caused by the immune response increases blood flow to the tissue delivering eager cellular reinforcements that have a futile anticipation of battle with phantom microbial invaders. It takes a while for the cells to embarrassingly realize their mistake and allow everything to settle down.

Medical authorities report that food allergies can result in varied symptoms and severity, which typically occur within a few hours of ingestion of the food [6, 10, 11]. The body systems affected include the skin (hives and swelling), gastrointestinal tract (vomiting and stomach cramps), respiratory tract (shortness of breath, wheezing, cough), and the cardiovascular system (weak pulse) [6, 12, 13]. In rare instances, severe food allergies result in anaphylaxis, a potentially life-threatening condition that sends the body into shock. Medical authorities note that specific food allergies usually occur in association with other forms of allergy. Infants with eczema are at higher risk of food allergy and asthma (citations in [14]), while 10–15% of infants who are allergic to cow’s milk are also allergic to soy [15]. The immune system works in mysterious ways! The factors driving the increased incidence of food allergies are still unclear, although there is a long list of suspects.

**Changing Recommendations of Health Authorities**

Most national health authorities recommend that, ideally, infants should be introduced to solid foods after exclusive breast feeding for the first four to six months [3]. In the year 2000, the American Academy of Pediatrics recommended delays for the introduction of foods potentially causing allergies in at-risk infants i.e., infants with multiple allergies or having at least one parent with an allergy [16]. This included delays to 1 year of age for dairy products, 2 years for eggs, and 3 years for peanuts, nuts, and fish. The rationale, with little or no supportive scientific evidence, was that the avoidance of allergenic foods during the critical period when the infant’s immune system is developing tolerance to newly introduced foods (around 4–6 months of age) would decrease the incidence of food allergies. However, after the adoption of these recommendations, the incidence of food allergies in infants kept increasing [2]. The American Society of Pediatrics in 2008 then amended its earlier recommendations based on a consensus of new scientific advice that concluded there was insufficient scientific evidence for benefit to at-risk infants from the delayed introduction of allergenic foods [17-20]. The recommendation also applied to the general population of infants (citations in [12]). More recently, Larson and colleagues confirmed this conclusion based on a retrospective analysis of 14 large-scale clinical investigations [6]. Strikingly, scientists now report that the introduction of peanuts and eggs to at-risk and general populations of infants aged 4–6 months decreases the incidence of corresponding allergic responses (citations in [12]). Scientific evidence has a habit of turning up the unexpected! For these reasons, most infant feeding guidelines from health
authorities indicate that “parents should not delay introduction of ‘allergenic’ foods beyond 4–6 months, provided the children are developmentally ready [21-23].”

**Allergy to Cow’s Milk**

The Australasian Society of Clinical Immunology and Asthma (ASCIA) provides useful information about cow’s milk allergy. ASCIA explains that cow’s milk allergy is not the same as lactose intolerance, a common misconception, and it affects about 1 in 50 infants, with most outgrowing the allergy by the age of 3–5 years [13]. They note the substantial evidence that cow’s milk allergy is an inflammatory response to proteins present in cow’s milk, and that the allergy symptoms occur within 15 minutes to two hours of exposure to the milk. The symptoms include hives, swelling (lips, tongue, face, or eyes), vomiting, diarrhea, and noisy breathing [13].

Tran and colleagues, using a population of over 2,000 children, concluded that delaying the introduction of cow’s milk beyond one year of age was associated with increased risk of milk protein allergy [21]. Despite this conclusion, and the similar scientific information available for other food allergies, health authorities still recommend the delay of the introduction of cow’s milk to infants until after 12 months of age (9 months in Canada). This recommendation has not changed over the last 18 years [24]. However, there is a strong reason to retain the recommendation, and it has no relationship with allergy. It is primarily related to iron deficiency.

**Too much Calcium and Not Enough Iron at a Critical Time**

Many scientists report that infants younger than 12 months have a big demand for iron to adequately support their growth and development [24-27]. Iron is essential for forming red blood cells that carry oxygen, and for myriad biochemical reactions making essential molecules inside cells. Medical researchers emphasize that infants during this period are at higher risk of iron deficiency (anemia) [24-27]. Although the energy contents of cow and human milks are similar, cow’s milk has much more protein and calcium but less iron [28]. The higher calcium level in cow’s milk also compounds its low level of iron, as calcium decreases the ability of an infant to absorb ingested iron [28]. This is not an issue at later ages when there are multiple dietary sources of iron and it is more efficiently absorbed by the gut. Consequently, clinicians warn that infants before 12 months of age and after cessation of breast feeding can become deficient in iron if they are fed exclusively on cow’s milk (formula milk is usually fortified with iron) [24, 26, 27]. The current health authority recommendation in many countries to delay the introduction of cow’s milk until infants are aged 12 months is based on the need to provide adequate amounts of iron to these young infants. Serendipity is amazing. The original recommendation in 2000 to delay the introduction of cow’s milk to infants until 12 months of age was partially based on the false expectation of avoiding allergy to cow’s milk, but the recommendation helped prevent anemia in young and vulnerable infants.

**Implications**

For parents, it is tough navigating the complex and changing maze of dietary recommendations for infants. The current challenge for health authorities is to weigh the quality of scientific evidence and then reach a consensus recommendation; all pieces of evidence are not of equal value. Presently, there is a strong scientific consensus that the delayed introduction of potentially allergenic foods to the general population of infants beyond 12 months does not decrease their risk of allergies, and in some cases may increase risk. The recommended delay in the introduction of cow’s milk protein to infants until they are older than 12 months ensures that younger infants gain sufficient iron from their formula or breast milk diet to support their growth, but it does not diminish the risk of allergy to cow’s milk. The recommendation for cow’s milk may need to be modified. Cow’s milk should not replace infant formula or breast milk until after 12 months of age, but there should be earlier exposure of infants to small amounts of cow’s milk, which may decrease their risk of developing allergy to cow’s milk.

Goat’s Milk: An Easily Digestible and Hypoallergenic Option

- Goat’s milk can sometimes be consumed by people who are allergic to cow’s milk, and it may be easier for the body to digest and absorb.
- The lower levels of a protein called alphaS1-casein in goat’s milk compared with cow’s milk explains much of goat’s milk hypoallergenic qualities.
- The iron and calcium components of goat’s milk have been found to be easier to absorb than those of cow’s milk.
- Goat’s milk is higher in fat and calories than cow’s milk.

Goats were one of the first animals to be domesticated [1], and research into the health implications of consuming goat’s milk has been published in academic journals for more than a century [2]. Yet new findings appear all the time. In the past year, for example, computational approaches have been applied to the study of bioactive peptides that are released when we digest goat’s milk—and levels of various anti-inflammatory components in goat’s milk have been measured. Broadly speaking, goat’s milk main benefits are that it prompts fewer allergic responses than cow’s milk and is more easily digested and absorbed. For
these reasons, its consumption is increasing all over the world.

That is not to say that goat’s milk is preferable to cow’s milk in every respect. Whether switching to it is worthwhile depends on your health status. Although goat’s milk is often an option for those with cow’s milk allergies, it is also rather high in fat (it contains 3.8% fat [3] compared with the 1% of cow’s milk) so is probably not a good option for people struggling with their weight. Moreover, pregnant women should take note that goat’s milk contains very little folic acid, vitamin B6 or B12, all of which are important for infant development.

Nonetheless, the main reason that goat’s milk is often well tolerated by people who struggle with cow’s milk allergies is its typically lower levels of a protein called alphaS1-casein. There are many variants of this protein, and the particular versions that appear in any mammal’s milk depend on the alphaS1-casein alleles (versions of a gene) of that animal. AlphaS1-casein is the major protein in cow’s milk, but, when it comes to goat’s milk, the title normally goes to a different protein, beta-casein. Still, goat’s milk has widely varying levels of alphaS1-casein, and some breeds—for instance, Alpine and Garganica goats—are often selectively bred on this basis [4]. The generally smaller amounts of alphaS1-casein in goat’s milk compared with cow’s milk means fewer digested particles from this protein pass through the gut wall and bind to antibodies called IgEs—the interaction that prompts the symptoms of milk allergy [4].

There are, of course, other molecules that lie behind goat’s milk hypoallergenic properties. Next to cow’s milk, it contains less beta-lactoglobulin, another allergen to some people, and it appears to stimulate the production of interleukin-10, a molecule that quells inflammation [4]. A few studies have analyzed the medium-length sugar molecules—oligosaccharides—in goat’s milk, and reported that these, too, have an anti-inflammatory effect in rats with induced colitis (which are often considered a model for inflammatory bowel disease in humans) [5, 6]. Moreover, a team of researchers based in Turkey has recently found levels of adipokines—anti-inflammatory molecules such as leptin—in goat’s milk that may contribute significantly to its much lesser allergenic effect than cow’s milk [7].

So why is goat’s milk more easy to digest than cow’s milk? This, too, is down to casein proteins—casein curd from goat’s milk is usually softer than the casein curd of cow’s milk—but also down to differences in the two milks’ fat component [8]. Goat’s milk has a lot of fatty acids whose chemical structures have medium-length carbon tails. This structural fact, in some ways, characterizes goat’s milk: three fatty acids—caprylic, caprylic and capric—are named after goats. As a result of its fatty acid composition, goat’s milk has smaller fat globules than cow’s milk, and this makes for better-dispersed fat globules. (What’s more, unlike goat’s milk, cow’s milk also contains a protein that encourages fat globules to collect, called agglutinin.) Because small fat globules have more surface area than large ones for any given total amount of fat, the emulsion structure of goat’s milk facilitates more digestive enzymes finding something to chew on [8].

Better digestion promotes better absorption. Overall, the evidence suggests that both calcium and iron appear to be better absorbed by the body from goat’s milk than cow’s milk. Back in the year 2000, a group at the University of Granada, in Spain, tested whether this was true in rats [9]. They fed rats a “standard diet,” a goat’s milk-based diet, or a cow’s milk-based diet, and then analyzed the rats’ body compositions. The results for calcium absorption were impressive: the calcium content of the animals’ femurs, sternums and longissimus dorsi muscles (a muscle running the length of the back) was higher among the rats fed the cow’s milk diet than the standard diet, yet higher still among rats fed the goat’s milk diet.

The same experiment did not find a difference in iron absorption between the two milk diets. But research conducted during the 18 years since has proposed goat’s milk as a possible treatment for anemia. Reviewing eight studies of iron availability and absorption interference, Nurul Nadiah Mad Zahir and colleagues concluded that “iron deficient rats treated with goat’s milk showed increased hemoglobin regeneration efficiencies... evidenced by increased serum hemoglobin, red blood cell count, packed cell volume...” [10]. These studies show two more key findings. The first is that a receptor in the small intestine—an ion transporter called divalent metal transporter 1—tends to be up-regulated in rats that have consumed a goat’s milk-based diet. This receptor is linked to the production of new red blood cells. The other important finding is that goat’s milk diets appear to lead to higher levels of iron stores in bodily
organs like the liver, spleen and bone marrow.

Goat’s milk certainly does not out-perform cow’s milk in every respect, but it does offer several advantages for people with cow’s milk allergies, and could help those who need to lay more calcium on their bones. It’s also a relatively under-researched substance. With more than 500 goat breeds in the world, and 95% of the global goat population in developing countries, there is plenty of science left to do and often not enough scientists situated in the right places to do it. Appetites for goat’s milk in richer countries are swelling. And even if it’s not to your palette, or the high fat content puts you off, one can now purchase goat-milk tablets and goat-milk powder as a nutritional supplement.


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