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Review Article

# Fat, demented and stupid: An unrecognized legacy of pediatric urology?

Christopher S. Cooper

Department of Urology, University of Iowa, Iowa City, IA, USA

Correspondence to: Christopher S. Cooper, University of Iowa, Department of Urology, 200 Hawkins Dr., 3 RCP, Iowa City, IA, 52242-1089, USA, Tel.: +1 319 384 8299; Fax: +1 319 356 3900

christopher-cooper@uiowa.edu (C.S. Cooper)

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**Summary**
The human body is an unfathomably intricate structure consisting of many connected and intertwined systems. This makes it impossible for therapeutic interventions to selectively target only one physiologic system without some impact or side effects on all the other systems. The resiliency of the human body modifies and disguises side effects, some of which may be undetectable for years and not apparent without scientific investigation.

Pediatric urologists employ relatively few medications for the common conditions they treat and in general these consist of antibiotics, anticholinergics, and anesthetics. Although harm from early side effects is well recognized, recent medical literature suggests there may be other side effects of these common interventions that aren't as well recognized.

Antibiotics have been added to livestock feed as growth promoters for three-quarters of a century. Antibiotics alter the microbiota of the intestinal tract and these alterations have been demonstrated to impact growth, metabolism, and the risk of obesity in animals and humans. To date, the long-term impact of daily antibiotic prophylaxis in children with such pediatric urology conditions as vesicoureteral reflux or prenatal hydronephrosis have not been published. Similarly, there are no studies assessing long-term effects of anticholinergic use on cognition in children despite research demonstrating an increased risk of dementia in adults using anticholinergics. Research in animals and children recently led the FDA to issue a warning regarding the risk of lengthy use of general anesthesia on cognitive development in children.

**Conclusions**
This review raises the possibility that antibiotics in children may alter growth, anticholinergics may increase their risk of dementia later in life, and anesthetics may impair their cognitive development. The possibility of such an unrecognized legacy from current therapeutic interventions should give all physicians, including pediatric urologists, pause for consideration before electing any intervention, no matter how routine or currently well accepted.

## Introduction

Physicians attempt to help their patients and do no harm. Pediatric urologists employ relatively few medications for the common conditions they treat and in general these consist of antibiotics, anticholinergics, and anesthetics. These medications undoubtedly help many children, and harm from early side effects is well recognized. However, given the complexity, intricacy and connectivity of the human body, any intervention, no matter how targeted, affects multiple and perhaps all of the body's physiologic systems. In addition, just as removing the tooth from one gear in a watch may ultimately lead to stress and breakage on it and the other parts, the total impact of medical intervention may not be readily evident. The resiliency of the human body helps disguise both short- and long-term side effects of the physician's interventions. The pediatric urologist, and all physicians, must constantly and humbly weigh the potential of such unrecognized and long-term systemic side effects when considering use of any of our relatively crude interventions no matter how well accepted and tolerated they currently seem. Recent medical literature suggests that antibiotics in children may alter growth, anticholinergics may increase the risk of dementia, and anesthetics may impair cognitive development. These possibilities raise the concern of an unrecognized legacy generated from common pediatric urologic interventions.

## Antibiotics

Antibiotics kill bacteria and oral antibiotics impact the microbiota of the intestinal tract. One aspect of this impact of antibiotics on the microbiota, widely recognized in pediatric

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urology, is the development of resistant bacteria in patients with breakthrough urinary tract infections. Reported rates of developing resistant bacteria in children on prophylactic antibiotics range from 3 to 24 times the rate compared to children not receiving prophylactic antibiotics [1–5].

The microbiota of the intestinal tract is a highly diverse and complex ecosystem containing 500–1000 species; in fact, 90% of all cells in the human body are bacterial. The microbiota plays a role in many normal functions including enhancement of host digestion, energy turnover, absorption of nutrients, barrier against pathogens, and development of the immune system [6]. Alteration of the microbiota by antibiotics or other means, including diet, may affect these normal functions. A change in the microbiota has been associated with increased risk of developing obesity in animal models and in human studies [7]. Obese mice and people frequently have higher Firmicutes/Bacteroidetes ratios in their microbiota, and the microbiota is different in obese and lean adult human twins [8].

The impact of oral antibiotics on animal growth has been recognized for many years. Over 70 years ago, Moore et al. [9] discovered that sulfonamide administration was associated with a twofold increase in weight in chicks. This increase in weight is independent of feed intake and in 1951 the FDA legalized the addition of antibiotics to animal feeds [10,11]. Greater responses in animal weight gains occur with antibiotic exposure earlier in life [6,12]. Mice given antibiotics have alterations in their microbiome as well as in carbohydrate and lipid metabolism and an increased adiposity. Further studies in mice demonstrate that a fecal transplant with stool from humans can transfer either an obese or lean phenotype from the human to the recipient mouse, further demonstrating the impact of the microbiota on metabolism and weight [13,14].

Multiple studies in humans demonstrate that short-term antibiotics may lead to persistent changes in the human gut microbiota [15]. The impact of antibiotics on the healthy human's weight was first demonstrated in an interesting study by Haight and Pierce in 1954 [16]. In this study Navy recruits were "selected immediately upon their arrival and formation on the station" because the investigators "recognized that there was a unique opportunity to observe the influence of prolonged antibiotic administration on the weight behavior of healthy young males." The recruits were randomly placed into three groups of 110 men each and received either a placebo, penicillin (PCN) (100,000 U), or tetracycline (250 mg) every morning for 7 weeks. The investigators demonstrated a significant ($p < 0.05$) weight gain and percentage of medico-actuarial standard weight for age in those receiving antibiotics compared to placebo.

More recent studies have demonstrated significant weight gain in humans treated with antibiotics, but the majority of these studies involve patients with significant medical illnesses such as cystic fibrosis [7]. Trasande et al. [17] noted that infants who received a course of antibiotics by 6 months of age more frequently developed an increased body mass and had significantly increased risk of being overweight as toddlers at 38 months than infants that did not receive antibiotics (OR 1.22; $p = 0.029$). An electronic health record review of 64,580 children at the Children's Hospital of Philadelphia demonstrated an increased risk of developing childhood obesity associated with both broad-spectrum antibiotics and cumulative exposure for those receiving four or more courses of an antibiotic [18]. In the largest series to date, with a review of 163,820 children between 3 and 18 years of age, Schwartz et al. [14] demonstrated both a persistent and a progressive weight gain with higher cumulative antibiotic exposure. In this study, weight gain was greatest with macrolides but was also seen with penicillin and cephalosporins.

To date, the long-term impact of daily prophylactic antibiotics on weight gain and growth in relatively healthy children with pediatric urologic conditions such as prenatal hydronephrosis or vesicoureteral reflux remains undetermined. In addition, the full impact of prophylactic antibiotics in these children on their microbiota and its multiple other functions including alterations in the immune system such as allergies should be investigated. Given the data presented above, the recent trend toward less universal and more selected and limited use of prophylactic antibiotics based on individual risk assessment is prudent [19].

## Anticholinergics

Anticholinergics are commonly prescribed for children with overactive bladders. Children with neurogenic bladders are routinely maintained on anticholinergics for decades. Even children with lower urinary tract symptoms due to non-neurogenic bladder overactivity may be prescribed anticholinergic medications for years [20]. Early central nervous system side effects from anticholinergics, including personality changes, confusion, headache, somnolence, dizziness, or hallucinations, are well recognized by pediatric urologists. These side effects are considered reversible and pediatric urologists routinely warn parents to watch for such side effects. If these side effects are recognized the medication dosage can be decreased or stopped completely.

Data now suggest the possibility that anticholinergics may cause long-term effects on cognition. Animal models demonstrate that reduced cholinergic transmission increases B-amyloid concentrations in the brain which is associated with dementia [21,22]. Several cohort studies have demonstrated an increased risk of dementia in adults taking long-term anticholinergics. One recent cohort study in adults concluded that a person taking an anticholinergic, such as oxybutynin, 5 mg/day, for more than 3 years had a greater risk for dementia [23]. This study demonstrated a 10-year cumulative dose–response with anticholinergics and the development of dementia ($p < 0.001$). The authors advised prescribers to use the lowest effective dose and discontinue therapy if ineffective. They also advised informing patients about this potentially modifiable risk and allow them to choose alternative products to minimize their overall anticholinergic use. Although this observational study cannot prove cause and effect, it did show an increased risk (HR 1.54, 1.21–1.96) with increased dosage. For the pediatric urologist, what makes this study even more worrisome is that a dose of 5 mg/day of oxybutynin placed these adult patients into the highest risk group and it is not uncommon for children with smaller body mass to be on an even greater dosage of anticholinergics.

To date, there are no data on whether anticholinergic medications affect a child's developing nervous system. It

is possible that the resiliency of the developing nervous system in children is such that there is no long-term impact of anticholinergics in this population. However, studies assessing long-term effects of anticholinergic use in childhood need to be performed as "the absence of evidence is not evidence of absence [24]".

Until definitive assessment of the potential risks of anticholinergics is performed, they must be at least considered before prescribing these medications. In addition, this concern emphasizes the importance of initial non-pharmaceutical urotherapy in children with lower urinary tract symptoms and consideration of alternative treatments to anticholinergics such as neuromodulation [25,26].

## Anesthetics

Since 1999, there has been growing concern and evidence that general anesthesia is a risk for impaired neurodevelopment in children [27]. Animal studies demonstrate central nervous system neurotoxicity as well as long-term adverse changes in behavior, learning, and memory following general anesthesia exposure lasting over 2 h in early life [27—29]. On the other hand, the interim results of the multi-institutional General Anesthesia Compared to Spinal Anesthesia (GAS) study that randomized infants less than 60 weeks to general or spinal anesthesia for hernia repair did not show an increased risk following a brief general anesthetic (median duration was 54 min) [30]. Of note, the authors concluded that reassessment at 5 years of age would be necessary for definitive conclusions and that the trial "does not rule out possibility that longer or many exposures to anesthesia in early childhood can cause neurodevelopmental changes." The Pediatric Anesthesia Neurodevelopment Assessment (PANDA) study produced similar findings in a sibling-matched cohort study comparing neurocognitive and behavior outcomes at 8—15 years of age in children who underwent a single exposure to general anesthesia for inguinal hernia surgery before 36 months of age [31]. The median anesthetic exposure in this study was 80 min. In another cohort study of 28,366 children who underwent surgery before primary school compared to 55,910 unexposed children, a statistically significant increase in developmental vulnerability was detected (25.6% vs. 25.0%; $p = 0.047$); however, this was not thought to be clinically significant [29]. The duration of anesthesia in these children was unspecified but a majority of these procedures were brief, including myringotomies, tonsillectomies, and circumcisions, and no risk association was seen with an increase in number of operations in this study. In a different cohort study of 18,056 children exposed to general anesthesia compared to 13,586 non-exposed children the authors did note that a single exposure to general anesthesia between 2 and 4 years of age was significantly associated with an increased risk of deficits in communication/general knowledge and language/cognition during kindergarten [28].

In December 2016, the FDA released a new warning stating that repeated or lengthy use of general anesthetic and sedation during surgeries or procedures in children younger than 3 years may affect the development of children's brains [32]. The warning notes that studies in animals show the use of general anesthetic for more than 3 h caused widespread loss of nerve cells in the brain. The announcement also notes that further research is needed to fully characterize how early-life anesthetic exposure affects children's brain development.

Although strong evidence of significant clinical impact following general anesthesia in children is lacking at this time, it seems reasonable to assume that general anesthesia is not beneficial to the developing brain and likely causes some degree of harm. The studies noted above, along with the recent FDA warning, reinforce the common pediatric urology practice of weighing the risks versus benefit of surgical intervention and avoiding unnecessary operations. In addition to considering the optimal timing for surgical interventions, this information should also encourage pediatric urologists and anesthesiologists to consider techniques that minimize the length of anesthetic exposure. Such considerations may result in limiting anesthesia delivery for infants and young children to the most time-efficient anesthesiologists. These considerations may also limit procedures and techniques that require additional time such as caudal blocks instead of local blocks or minimally invasive laparoscopic or robotic approaches instead of an open approach for certain conditions.

## Conclusion

Dean Wormer was a fictional character in National Lampoon's movie "Animal House" who told one of his students, Flounder, a universal truth: "Fat, drunk, and stupid is no way to go through life, son" [33]. Flounder promptly responded by throwing up on the Dean. Although the concerns of generating an unrecognized pediatric urology legacy of "fat, demented, and stupid" raised in this review are hyperbole and not meant to induce emesis among pediatric urologists, it is hoped these concerns will give the pediatric urologist pause for thought (and perhaps just a bit of nausea) regarding therapeutic interventions. Any resemblance of Dean Wormer or Kent Dorfman (a.k.a. "Flounder") to past or present pediatric urologists is sad and unintentional.

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## Conflict of interest

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