Important Pediatric Urology Articles of 2018 - 2019

Michael P. Kurtz, MD, MPH
Assistant Professor of Surgery, Harvard Medical School
Department of Urology, Boston Children’s Hospital
What’s “Top” when accounting for taste?

...AND ADD SUGAR TO TASTE.
Web of Science to the rescue!
$R^2 = 0.108$

~90% predicted citation volume *not* due to month of publication
Game plan

• We’ll discuss:
  – The **highest cited, highest altmetric** ranked papers in our field of pediatric urology
  – Very few from Journal of Urology (by chance) \(\rightarrow\) ↓↓ overlap with the AUA annual summary
  – No reviews

  You’ll be surprised!
• UTIs account for ~90% of all serious bacterial infections (defined as UTIs, bacteremia, and bacterial meningitis) in febrile infants 60 days of age or less

• Unclear how reliable a urinalysis alone is in diagnosing urinary tract infection in neonates
Accuracy of the Urinalysis for Urinary Tract Infections in Febrile Infants 60 Days and Younger

Leah Tzimenatos, MD,1 Prashant Mahajan, MD, MPH, MBA,2 Peter S. Dayan, MD, MSc,3 Melissa Vitale, MD,4 James G. Linakis, MD, PhD,5 Stephen Blumberg, MD,6 Dominic Borgialli, DO, MPH,7 Richard M. Ruddy, MD,8 John Van Buren, PhD,4 Octavio Ramilo, MD,1 Nathan Kuppermann, MD, MPH,9,10 for the Pediatric Emergency Care Applied Research Network (PECARN)


• Wait … *don’t you always get a urine culture?*
  – >20% of patients will *not* get urine cultures (despite guidelines)
  – What do you do before the culture is back?
  – What about lab sabotage?
Solution?

- Lots of babies!
- Ages 0-60 days
- 4147 infants, 298 with UTI
  - 26 centers across the USA
  - 73% of the cohort is female
<table>
<thead>
<tr>
<th>Identification of any UTI (N = 289)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any LE, n = 4147</td>
<td>0.92 (0.89–0.95)</td>
<td>0.96 (0.95–0.96)</td>
</tr>
<tr>
<td>Nitrites, n = 4147</td>
<td>0.38 (0.33–0.44)</td>
<td>0.99 (0.99–1.00)</td>
</tr>
<tr>
<td>Pyuria, &gt;5 WBCs/HPF, n = 4100</td>
<td>0.82 (0.77–0.86)</td>
<td>0.94 (0.93–0.94)</td>
</tr>
<tr>
<td>LE or nitrites, n = 4147</td>
<td>0.93 (0.90–0.96)</td>
<td>0.95 (0.95–0.96)</td>
</tr>
<tr>
<td>Aggregate urinalysis (LE or nitrites or pyuria), n = 4147</td>
<td>0.94 (0.91–0.97)</td>
<td>0.91 (0.90–0.91)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Identification of UTI with bacteremia (N = 27)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any LE, n = 3885</td>
<td>1.00 (0.87–1.00)</td>
<td>0.96 (0.95–0.96)</td>
</tr>
<tr>
<td>Nitrites, n = 3885</td>
<td>0.41 (0.22–0.61)</td>
<td>0.99 (0.99–1.00)</td>
</tr>
<tr>
<td>Pyuria, &gt;5 WBCs/HPF, n = 3858</td>
<td>0.77 (0.55–0.92)</td>
<td>0.94 (0.93–0.94)</td>
</tr>
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</tbody>
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<table>
<thead>
<tr>
<th>Identification of UTI without bacteremia (N = 262)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any LE, n = 4120</td>
<td>0.92 (0.88–0.95)</td>
<td>0.96 (0.95–0.96)</td>
</tr>
<tr>
<td>Nitrites, n = 4120</td>
<td>0.38 (0.32–0.44)</td>
<td>0.99 (0.99–1.00)</td>
</tr>
<tr>
<td>Pyuria, &gt;5 WBCs/HPF, n = 4078</td>
<td>0.82 (0.77–0.87)</td>
<td>0.94 (0.93–0.94)</td>
</tr>
<tr>
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</tr>
</tbody>
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One-liner

In infants <60 days, a broad definition of UTI on UA works

– *Any* leukocyte esterase
– *Any* nitrite
– *>5 WBC* / hpf

→ You’ve got a UTI (patient will grow >50K uropathogen)
→ At least 94% sensitivity and 91% specificity
→ Still check a urine culture
Has the robot caught up? National trends in utilization, perioperative outcomes, and cost for open, laparoscopic, and robotic pediatric pyeloplasty in the United States from 2003 to 2015

Briony K. Varda a, Ye Wang b, Benjamin I. Chung c, Richard S. Lee a, Michael P. Kurtz a, Caleb P. Nelson a, Steven L. Chang b

• Nationally representative sample of U.S. hospitalizations between 2003 and 2015
• 11,899 pyeloplasties were performed: 75% open, 10% laparoscopic, and 15% robotic
• Analyzed usage, costs, using propensity matching and a clustered design
Pyeloplasties over time

Open
Pure Lap
Robotic-assisted


Graph showing the number of pyeloplasties performed over time, with a decline in open procedures and an increase in robotic-assisted and pure laparoscopic procedures.
Older patients are more likely to have a robotic approach.
Robotic versus open costs

- Robotic surgery is associated with:
  - Shorter LOS, prolonged operative time, comparable complications, and higher costs (equipment, OR costs)

Table: Propensity-score weighted multivariable-adjusted analyses for perioperative outcomes and cost associated with robotic pyeloplasty (as compared with the open approach).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged LOS (&gt;2 days)</td>
<td>0.14</td>
<td>(0.05–0.38)</td>
<td>0.001</td>
</tr>
<tr>
<td>Prolonged OT (&gt;200 min)</td>
<td>5.4</td>
<td>(3.1–9.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Complications</td>
<td>0.80</td>
<td>(0.34, 1.9)</td>
<td>0.62</td>
</tr>
<tr>
<td>Open</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robotic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median cost (USD)</td>
<td>$10,817</td>
<td>$11,877</td>
<td>0.03</td>
</tr>
</tbody>
</table>

LOS = length of stay; OT = operative time.
• Hypothalamic-pituitary-gonadal axis is **activated in infancy**
  – Peaks when the infant is between **1 week and 3 months of age**
• Can we use hormonal measures to develop a nomogram?
• 1840 infants from healthy cohorts in Denmark
• 27 infants with DSD aged 2-5 months
  – LH, FSH, testosterone (T), estradiol, sex hormone– binding globulin (SHBG), inhibin B, anti-Mullerian hormone (AMH), dehydroepiandrosterone (DHEA), DHEA sulfate (DHEAS), 17-hydroxyprogesterone (17-OHP), androstenedione, and LH/FSH ratio.
LH and FSH concentrations showed overlap between sexes, with LH being highest in boys and FSH being highest in girls (Female = FSH)

- The LH/FSH ratio separated infant boys from girls with minimal overlap at a cutoff value of 0.32
- Inhibin-B and AMH concentrations were higher in boys
Sex Differences in Reproductive Hormones During Mini-Puberty in Infants With Normal and Disordered Sex Development

Trine Holm Johanssen,1,2 Katharina Maria Main,1,2 Marie Lindhardt Ljubicic,1,2 Tina Kold Jensen,1,2,3,4 Helle Raun Andersen,3 Marianne Skovsgaard Andersen,5 Jørgen Holm Petersen,1,2,6 Anna-Maria Andersson,1,2 and Anders Juul1,2

Figure 1. Serum concentrations of LH, FSH, and the LH/FSH ratio in boys (blue) and girls (red) during mini-puberty. The concentrations are shown on a log with base 10 (log10)-transformed y-axis (dotted lines, LOD; solid lines, cutoff value for separating boys from girls; %, percentage of measurements below LOD).
GENERAL QUALITY OF CHARTS AND GRAPHS IN SCIENTIFIC PAPERS

POWERPOINT/MSPAINT ERA
Sex Differences in Reproductive Hormones During Mini-Puberty in Infants With Normal and Disordered Sex Development

Trine Holm Johannsen,1,2 Katharina Maria Main,1,2 Marie Lindhardt Ljubicic,1,2 Tina Kold Jensen,1,2,3,4 Helle Raun Andersen,3 Marianne Skovsager Andersen,5 Jørgen Holm Petersen,1,2,6 Anna-Maria Andersson,1,2 and Anders Juul1,2
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[Graphs showing inhibin B and AMH levels over age (months)]
• Infants with compete androgen insensitivity
  – LH/FSH ratios were in the range of control males
• Klinefelter, Turner, 45,X/46,XY mosaicism
  – LH/FSH ratios matched the gender of rearing
• In mini-puberty, “the classifiers that best separated sex in mini-puberty were AMH, LH/FSH ratio, and T”
AAP guidelines changed regarding infant UTI workup in September of 2011

Study uses PHIS (~15% of pediatric hospitalizations) to examine the degree to which VCUGs ordered and anti-reflux operations performed changed after this release

Interrupted time series analysis
Sudden decrease in VCUG orders; new steady state afterward
National Trends in the Management of Primary Vesicoureteral Reflux in Children

Slow, steady decrease in treatment of primary VUR after guideline release
National Trends in the Management of Primary Vesicoureteral Reflux in Children

- Powerful association between guidelines and diagnostic studies
- More gradual impact on surgical procedures
- PHIS may not be ideal (inpatient, ambulatory surgery, emergency department and observation unit patient encounters) but impact is clear
Reduction and standardization of surgical instruments in pediatric inguinal hernia repair

- Authors set out to reduce surgical instrumentation by >25%
- Urology AND Pediatric Surgery
- >12 surgeons
- >32 nurses
- Can they do it?
Reduction and standardization of surgical instruments in pediatric inguinal hernia repair

• Began with observation
  – 12 pediatric urology cases
  – 44 general surgery cases
  – Urology had 96(!) instruments of which 69 were never used
  – General surgery had 51, of which 17 were never used
Reduction and standardization of surgical instruments in pediatric inguinal hernia repair

• Measured
  – Tray weights
  – Cycle time: how long it takes to prepare a sterile tray – rinse, sterilize, repack
    • Timing the same central supply worker to reduce variability

• Surveys for all participants
Reduction and standardization of surgical instruments in pediatric inguinal hernia repair

• Phase 1: Presentation, Survey all participants
  – The study team met weekly to discuss collected data, and to assure that ongoing, frequent informal interaction with all stakeholders took place to update them of findings and invite their input
  – Developed a tray of instruments used in >50% of cases

• Phase 2: Use the trays. Measure. Old trays on standby
Reduction and standardization of surgical instruments in pediatric inguinal hernia repair

• New tray = 28 instruments

• Results:
  • New tray cycle time = 5 minutes
    – Formerly was 8 minutes for general surgery, 11 minutes for urology tray
Reduction and standardization of surgical instruments in pediatric inguinal hernia repair

- Achieved through a PDSA (plan, do, study, act) cycle
- Authors address additional challenges. Not ideal for:
  - Teenagers
  - Two-incision orchidopexies
  - more peel packs available

Table 2  Post-standardization survey as to perception of post-standardization tray on actual practice and to ascertain need for additional instruments.

<table>
<thead>
<tr>
<th>Compared with unstandardized (old) tray, how would you rate the standardized (new) tray?</th>
<th>No difference</th>
<th>Better</th>
<th>Worse (prefer old tray)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nurses (32)</td>
<td>3%</td>
<td>91%</td>
<td>6%</td>
</tr>
<tr>
<td>Surgeons (12)</td>
<td>33%</td>
<td>60%</td>
<td>7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Do you routinely require additional instruments that are not available on new tray?</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>If you answered yes, are they readily available?</td>
<td>100%</td>
<td>0</td>
</tr>
</tbody>
</table>
Improved outcome at end of treatment in the collaborative Wilms tumour Africa project

Trijn Israels1,2 | Vivian Paintsil3 | Dalida Nyirenda4 | Francine Kouya5 | Glenn Mba Afungchwi6 | Peter Hesseling7 | Clara Tump8 | Gertjan Kaspers1,9 | Liz Burns10 | Ramandeep Singh Arora11 | George Chagaluka4 | Philippa Nana5 | Lorna Renner12* | Elizabeth Molyneux4*

- Malawi (Blantyre), Cameroon (Mbingo, Banso, Mutengene) and Ghana (Accra and Kumasi)
- 109 Pediatric urologists by the 2015 AUA census
• The Collaborative Wilms Tumour (WT) Africa Project implemented an adapted WT treatment guideline in sub-Saharan Africa as a multi-center prospective clinical trial.

• Collaborative project aimed to reduce both treatment abandonment and death during treatment to less than 10% for improving survival.

• Outcomes at 2 years.
1. Less toxic chemotherapy (lower dose doxorubicin)
2. Chemotherapy stratification, avoiding radiation
3. “Simple intervention”
   – free treatment for poor families to enable them complete treatment
   – social support, which included meals for patients and travel costs
   – if possible, a place to stay for poor families
• Unique challenges
• 10% of patients initially enrolled did NOT have a Wilms tumor after surgery
  – Due to poorer quality sonography
  – Burkitt lymphoma was the true diagnosis in half of those initially misdiagnosed with Wilms
**Improved outcome at end of treatment in the collaborative Wilms tumour Africa project**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All centres</th>
<th>2011–2012</th>
<th>2014–2015</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive, no evidence of disease</td>
<td>63 (52%)</td>
<td>90 (68%), P = 0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abandonment of treatment</td>
<td>28 (23%)</td>
<td>17 (13%), P = 0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death during treatment</td>
<td>26 (21%)</td>
<td>17 (13%), P = 0.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent disease or relapse</td>
<td>5 (4%)</td>
<td>8 (6%)</td>
<td>N.S.</td>
<td></td>
</tr>
<tr>
<td>Death other cause</td>
<td>0 (0%)</td>
<td>1 (1%), N.S.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>122 (100%)</td>
<td>133 (100%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Burnout in Urology: Findings from the 2016 AUA Annual Census

Amanda C. North,* Patrick H. McKenna, Raymond Fang, Alp Sener, Brian Keith McNeil, Julie Franc-Guimond, William D. Meeks, Steven M. Schlossberg, Christopher Gonzalez and J. Quentin Clemens

Bullitt, Warner Bros. 1968
The Triad of

- **Emotional exhaustion:** feeling emotionally overextended and exhausted by one’s work
- **Depersonalization:** an unfeeling and impersonal response toward recipients of one’s service, and
- **Decreased sense of personal accomplishment:** decreased feelings of competence and successful achievement in one’s work
Methods

- AUA Annual Census – 18.9% Response Rate (US Urologists)

MBI-Human Services Survey for Medical Personnel
1. I feel emotionally drained from my work.
2. I have accomplished many worthwhile things in this job.
3. I don't really care what happens to some patients.
38.8% of responding urologists reported burnout

Mid-career urologists were at highest risk

No racial, ethnic, gender differences

Working less hard appears to be protective
  – Seeing fewer than 50 patients per week
  – Working under a 40-hour week

Pediatric urology has the lowest rate of burnout (25%)
Good news?

• Previous reports in the AMA had suggested a 63.6% rate of burnout for urologists
  – This report is far lower
• Being a pediatric urologist is protective
• “Perhaps working with a specialized population helps physicians retain meaning in their work, with loss of meaning in one’s work a contributing factor for burnout.”
Not good news

AMA study found a 41% rate of burnout in 2011
→ Prevalence of burnout has increased by >50%

Under the Wave off Kanagawa (c1830-1832)
Katsushika Hokusai (c1830-1832)
• Literature search 2013 onward of pediatric urology articles using Intuitive Surgical robotic platform
• Examined authors COI disclosures vs Open Payments in CMS
• Analyzed 107 articles remained (267 distinct authors)
86 (80.4%) had at least 1 author with a history of payment from Intuitive Surgical

– Of these, 92% did not declare their COI

• Average payment of $3,594.15

• Articles with a first and/or last author with a history of payment were more likely to contain a favorable endorsement of robotic surgery
Receiving Industry Payments is Associated with Prescribing Habits of Tadalafil

Kevin J. Chua,* Gen Li, Peter J. Stahl and Elias S. Hyams

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CI 3.67–5.50, p < 0.001) but not for urologists (p = 0.922). Urologist prescription was not associated with increasing payment amount or greater number of payments. For primary care physicians there was an association of prescribing tadalafil with increasing payment amount (OR 1.01, 95% CI 1.00–1.02, p = 0.02) and increasing number of payments (OR 1.15, 95% CI 1.03–1.28, p = 0.01). There were weak but statistically significant correlations between claim count and payment amount for urologists and primary care physicians (r = 0.063 and r = 0.1, respectively, p < 0.05).
Assessment of Conflicts of Interest in Robotic Surgical Studies

Validating Author’s Declarations With the Open Payments Database

Sunil V. Patel, MD, MSc,*†‡ David Yu, MD,* Basheer Elsolh, MD,†
Ben M. Goldacre, MD, MSc,‡ and Garrett M. Nash, MD, MPH§

Results: A total of 458 studies (2253 authors) were included. Approximately, 240 (52%) studies had 1 or more author receive undeclared payments and included 183 where “no COI” was explicitly declared, and 57 with no declaration statement present. Moreover, 21% of studies and 18% of authors with a COI declared it so in a COI statement. Studies that had undeclared payments from Intuitive were more likely to recommend robotic surgery compared with those that declared funding (odds ratio 4.29, 95% confidence interval 2.55–7.21).
Compared open and MIS approaches for pediatric neuroblastoma and Wilms tumor

- National Cancer Data Base from 2010 to 2012
- Cases of neuroblastoma and WT in children ≤21 years old.
- 17% (98 of 579) underwent MIS, while only 5% of children with WT (35 of 695) had an MIS approach for tumor resection.
Propensity matched survival curves

A

Neuroblastoma

Survival (%)

Time (Years)

Log-Rank Test: $P=0.65$

B

Wilms tumor

Survival (%)

Time (Years)

Log-Rank Test: $P=0.96$
Most influential of all

Oral Antibiotic Exposure and Kidney Stone Disease

Gregory E. Tasian, Thomas Jemielita, David S. Goldfarb, Lawrence Copelovitch, Jeffrey S. Gerber, Qufei Wu, and Michelle R. Denburg

(<2% of cohort age <20 years)
Oral antibiotic exposure and kidney stone disease

- Association between 12 classes of oral antibiotics and nephrolithiasis in a population-based case–control study
- 13 million children and adults from 1994 to 2015 in the United Kingdom
Younger age of Abx \(\rightarrow\)
Higher odds stone formation
Sulfa drugs, younger age, recent exposure ...
Sulfa drugs, younger age, recent exposure ...
Antimicrobial Prophylaxis for Children with Vesicoureteral Reflux
Letters in Winning Word of Scripps National Spelling Bee correlates with Number of people killed by venomous spiders

\[ r = 0.806 \]
Per capita cheese consumption correlates with Number of people who died by becoming tangled in their bedsheets

\[ r = 0.941 \]
This effect is **real**

- Biologically plausible
- Exceptional epidemiologic methods (very well controlled)
- Temporal relationship is strong
- Seen across many agents
- Let’s see what the microbiome shows …