Top Ten Pediatric Infectious Disease Articles of 2017

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3/29/18

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Pediatric Infectious Disease

Telephone Consultations

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Top Ten Articles Presentation

- Subject
- Methods
- Results
- Conclusions
- Extras

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Article 10

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Effect of dilute apple juice and preferred fluids vs electrolyte maintenance solution on treatment failure among children with mild gastroenteritis

- Freedman SB, Wilan AR, Boutis K, Schuh S
- Alberta Children's Hospital
- JAMA 2016;315:1966-1974

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Apple Juice in GE-2
Methods-1

- Single center, randomized, single-blind, non-inferiority trial at ED of Toronto Sick Children's Hospital.
- Inclusion
  - Age 6-6-months + ≥ 8 kg weight.
  - ≥ 3 episodes of vomiting and/or diarrhea in preceding 24 hours.
  - <4 days of symptoms.
  - "Minimal dehydration"

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Apple Juice in GE-3
Methods-2

- "Minimal dehydration"
  - < 5 on Clinical Dehydration Score (Pediatrics 2008;122:545)
  - Capillary refill < 2 seconds.

TABLE 1 CDS[10]

Characteristic	Score of 0	Score of 1	Score of 2
General appearance	Normal	Thirsty, restless, or lethargic but irritable when touched	Drowsy, limp, cold, or sweaty; comatose or not
Eyes	Normal	Slightly sunken	Very sunken
Mucous membranes (tongue)	Moist	Sticky	Dry
Tears	Tears	Decreased tears	Absent tears

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Apple Juice in GE-4
Methods-3

- Random Assignment
  - ½ strength apple juice followed by "preferred fluids," or
  - Electrolyte maintenance solution only.
- Study solutions in identical containers.
- Protocol: 5 ml aliquots of fluids every 2-5 minutes; for vomiting: ondansetron.
- ED MD then makes further treatment decisions.

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Apple Juice in GE-5
Methods-4

- Caregivers then continued the fluid assignments at home to replace all losses: 2 ml/kg vomiting episode; 10 ml/kg diarrhea episode.
- Follow-up
  - Daily telephone contact by research RN.
  - Caregiver diary of follow-up care, MD visits, and frequency of symptoms.

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Apple Juice in GE-6
Methods-5

- Study Outcomes
  - Hospitalization or IV rehydration.
  - Unscheduled MD visits.
  - Protracted symptoms (≥3 episodes of vomiting or diarrhea in 24 hours occurring > 7 days after enrollment.
  - MD change in oral fluids.
  - ≥3% weight loss.
- Sample size to yield 80% power to detect a 7.5% difference.

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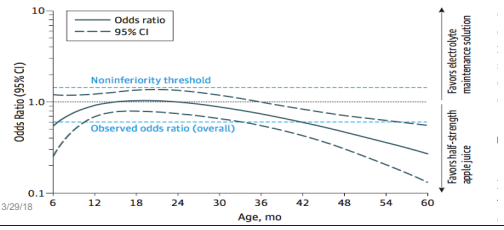
Apple Juice in GE-7
Results

- N = 647.

Figure 2. Treatment Failure Comparing Half-Strength Apple Juice/ Preferred Fluids Therapy and Electrolyte Maintenance Solution Groups as a Function of Age



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Apple Juice in GE-8 Conclusions

- Children with gastroenteritis and mild dehydration experienced fewer treatment failures with dilute apple juice + preferred fluid vs electrolyte maintenance solution.
- Absolute risk reduction = 8.3%.
- NNT = 12.
- Benefit greatest in age > 2 years.

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Extras

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Arch Dis Child 2014;99:878–880

- Comparison of ultra-rapid rehydration (50-60 ml/kg over 1 hour) with standard rehydration (over 3 hours) and oral/NG rehydration in moderate diarrheal dehydration
- No superiority could be demonstrated between ultra-rapid rehydration and either standard or oral/NG rehydration.

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Oral rehydration solution

- Commercial premixed
- WHO-ORS packets
  - Sold on Amazon.com

www.rehydrate.org

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Oral rehydration solution-2

- Homemade ($0.20 per liter)
  - 3/4 tsp salt
  - 1 tsp baking soda
  - 4 tbl sugar
  - 1 cup orange juice
  - 1 quart water
- *N Engl J Med* 1991;325:327 • *Pediatrics* 1992;89:980

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Homemade Oral Rehydration Solution Recipes		
Sugar and salt water	• 1 quart water • ¾ teaspoon salt • 6 teaspoons sugar • Optional: Crystal Light® to taste (especially lemonade or orange-pineapple flavors)	
Gatorade® G2	• 4 cups Gatorade® G2 (or one, 32 ounce bottle) • 1/2 teaspoon salt	
Chicken Broth	• 4 cups water • 1 dry chicken broth cube • ¼ teaspoon salt • 2 tablespoon sugar	**OR** • 2 cups liquid broth • 2 cups water • 2 tablespoon sugar
Tomato Juice	• 2 ½ cups tomato juice • 1 ½ cups water	
Homemade Cereal Based	• ½ cup dry, precooked baby rice cereal • 2 cups water • ¼ teaspoon salt • Combine ingredients and mix until well dissolved and smooth. Refrigerate. Solution should be thick, but pourable and drinkable.	

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Article 9

Faster clean catch urine collection (Quick-Wee method) from infants: randomized controlled trial

- Kaufman J, Fitzpatrick P, Tosif S, et al.
- Royal Children's Hospital, Victoria, Australia
- BMJ 2017;357:1341

Quick-Wee method-2
Methods-1

- Randomized, prospective, non-blinded superiority trial.
- Single tertiary pediatric ED.
- Inclusion
  - Age 1-12 months.
  - Urine sample required.
  - "Clean catch" deemed appropriate.
- Random assignment to Quick-Wee method or standard clean catch urine.

Quick-Wee method-3
Methods-2

- Standard Clean Catch
  - Clean genital orifice for 10 seconds.
  - Wait 5 minutes for baby to urinate.
- Quick-Wee Method
  - Clean genital orifice for 10 seconds.
  - Rub suprapubic area in a circular pattern with gauze soaked in cold saline for up to 5 minutes.

Quick-Wee method-4
Methods-3

- Outcomes
  - Voiding within 5 minutes.
  - Successful catch of voided urine.
  - Urine contamination on culture (= multiple colony types with primary organism non-pathogen)
  - Parent and provider satisfaction.
- Sample Size
  - Power of 80% to detect a 15% difference.

Quick-Wee method-5
Results-1

- N = 344.
- Male = 50%; female = 50%.
- 14% of babies had UTI ($\geq 10^5$ cfu/ml).
- Voiding < 5 minutes
  - Quick-Wee = 31%.
  - Standard = 12%.
- Successful Catch
  - Quick-Wee = 96%
  - Standard = 75%

Quick-Wee method-6
Results-2

- Contamination
  - Quick-Wee = 27%.
  - Standard = 45%.
- Satisfaction
  - Quick-Wee = "satisfied."
  - Standard = "neutral."

Quick-Wee method-7
Conclusions

- "Voiding stimulation methods such as Quick-Wee can enhance clean catch urine collection by increasing the speed and success of obtaining urine."
- AKA = "Brilliant!"

Extras

A new technique for fast and safe collection of urine in newborns

- Fernandez MLF, Merino NG, Garcia AT et al.
- University Infanta Sofia Hospital, Madrid
- *Arch Dis Child 2013;98:27-29*

Urine collection-2
Methods

- Prospective feasibility and safety study.
- Inclusion: infants ≤ 1 month who required a urine sample
- Technique: feed the baby; 25 min later, clean genitals; hold baby under armpits with legs dangling; rapid tapping on bladder for 30 sec; light circular massage of lumbar paravertebral zone for 30 sec; repeat until micturition

Urine collection-3
Results

- 80 consecutive infants: 31 girls and 49 boys; mean age 6 days.
- 86% success rate
- Mean time for sample collection was 57 sec. No difference between genders.
- Controlled crying occurred in all babies

Urine collection-4
Conclusions

- Midstream urine collection in infants is possible with minimum trauma 86% of the time.

Dipstick screening for urinary tract infection in febrile infants

- Glissmeyer EW, Korgenski EK, Wilkes J, et al
- University of Utah School of Medicine
- *Pediatrics 2014';133:e1121-e1127*

Dipstick screening for UTI-1
Methods-1

- Retrospective observational study.
- 23 Intermountain Healthcare hospitals.
- Inclusion
  - Febrile infants aged 1-90 days; 2004-2011.
  - Catheterized urine specimens obtained.
- All had urine dipstick, microscopic UA, urine culture.

Dipstick screening for UTI-2
Methods-2

- (+) UTI = ≥ 1 urine pathogen, each ≥50,000 cfu/ml.
- (-) UTI = <10,000 cfu/ml of organisms identified as skin or GU flora.
- (+/-) UTI = 10,000 – 49,999 cfu/ml of urine pathogen.
- Equivocal UTI were excluded from analysis.

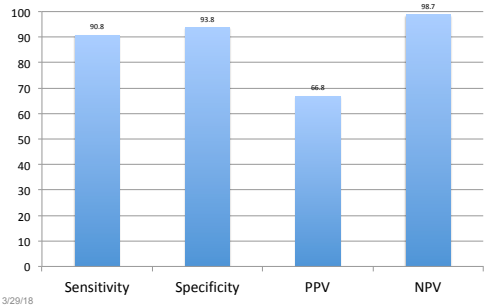
Dipstick screening for UTI-3
Methods-3

- (+) Dipstick = either LE (+) or NIT (+). (+) = > "trace."
- (+) Micro = >10 WBC/hpf or any bacteria seen.
- Sensitivity, specificity, PPV, NPV were calculated for each of the UA results.

Dipstick screening for UTI-4
Results-1

- 13,030 febrile infant encounters.
- 6536/13,030 (50%) had all urine studies
- After equivocal UCx excluded, 6394 enrolled infants were analyzed.
- 770/6394 (prevalence = 12%) had (+) UTI.

Dipstick screening for UTI-5
Results-2



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Dipstick screening for UTI-6
Results-3

- Likelihood Ratios
  - (+) Dipstick = 14.6.
  - (-) Dipstick = 0.1.
- Urine microscopy did not add any meaningful accuracy to dipstick alone.
- False positive screens were higher with urine microscopy: 8 infants had false positive micro testing for every 1 infant with true UT I not identified by dipstick.

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Likelihood Ratio

- The Likelihood Ratio (LR) is the odds that a given test result would be expected in a patient with the target disorder compared to the likelihood that that same result would be expected in a patient without the target disorder.
- References
  - Grimes DA, Schultz KF. Refining clinical diagnosis with likelihood ratios. Lancet 2005;365:1500-1505
  - McGee S. Simplifying likelihood ratios. J Gen Intern Med 2002;17:647-650
- Explanation and examples
  - http://www.cebm.net/index.aspx?o=1043
- Compute likelihood ratios
  - http://araw.mede.uic.edu/cgi-bin/testcalc.pl

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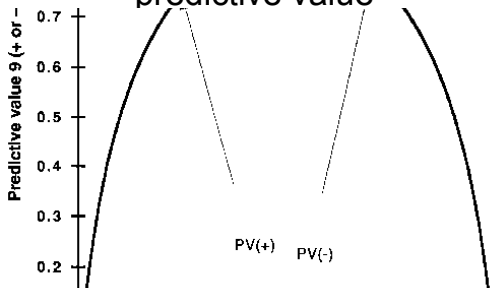
Effect of prevalence on predictive value



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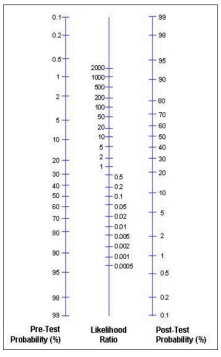
Likelihood Ratio

- http://araw.mede.uic.edu/cgi-bin/testcalc.pl



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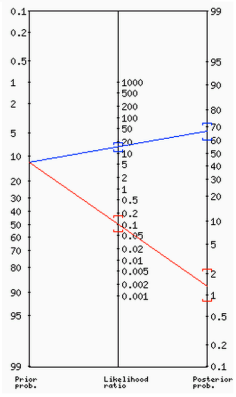

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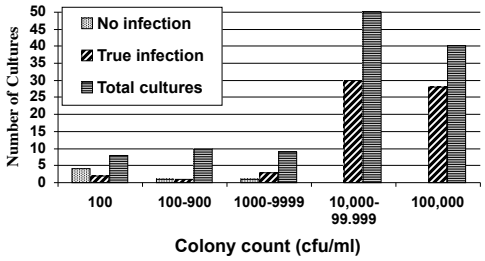
Dipstick screening for UTI-7
Results-4

- Fate of infants with (-) dipstick but (+) UCx
  - Age 1-28 days:
    - All febrile neonates were admitted to hospital with full sepsis workup and antibiotics.
  - Age 29-90 days (53 febrile infants):
    - 83% were admitted to hospital anyway and started on effective antibiotics.
    - 17% were sent home. All had (+) UCx by 24 hours and were treated with antibiotics.
    - Two (3.8%) had bacteremia; none had (+) CSF.

Dipstick screening for UTI-8
Conclusions

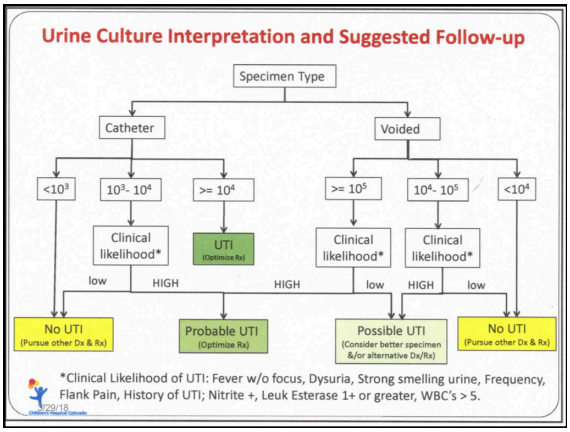
- These data comprise the largest study of urinary diagnostic testing in febrile infants < 90 days.
- No urine screening test has perfect accuracy.
- The use of urine dipstick testing alone, without microscopy, is an effective screening tool.
- Dipstick testing + use of likelihood ratios can enhance decision-making.

Urine culture
Definition of true infection-1



"True infection" = 1st: SBT (+); 2nd: Cath/ midstream(+)

Clin Pediatr 1977;16:698



Article 8

A randomized controlled trial of positioning for lumbar puncture in young infants

- Hanson AL, Schunk JE, Corneli HM, Sporano JV.
- Universities of Louisville and Utah Schools of Medicine
- Pediatric Emerg Care 2016;32:504-507

Lumbar puncture-2
Methods-1

- Randomized, prospective trial.
- Tertiary care pediatric ED.
- Inclusion
  - Age 1-90 days.
- Exclusion
  - Recent LP, coagulopathy, anatomical oddities.
- "Successful LP"
  - CSF < 10,000 RBC on attempts 1 or 2.

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Lumbar puncture-3
Methods-2

- Random assignment to either "lateral flexed" or "sitting flexed" positions.
- Subsequent provider questionnaire to assess other success techniques: e.g. anesthesia ("Tootsweet" 24% sucrose, topical numbing agents), early stylet removal.
- Samples size to provide 80% power to detect a 15% difference.

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Lumbar puncture-4
Results

- N = 167.
- Success Rates (attempts 1 or 2) - NS
  - Lateral flexed = 77%.
  - Sitting flexed = 72%.
- Success Rates (1st attempt) - NS
  - Lateral flexed = 62%.
  - Sitting flexed = 53%.

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Lumbar puncture-5
Conclusions

- "This randomized study found no statistically significant difference in LP success rate between the lateral and sitting positions."

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Analysis of infant lumbar puncture success rates
Sitting flexed versus lateral flexed positions

- Lanson AL, Ros S, Sporano J
- Loyola University Medical Center, IL
- *Pediatr Emerg Care 2014;30:311-314*

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Lumbar puncture-2
Methods

- Retrospective chart review.
- Age: 0-365 days.
- LP performed for any indication in ED.
- Data Gathered
  - Position during LP
  - Number of LP attempts
  - Success rates
  - Amount sufficient for culture & cell count
  - CSF RBC : <500 or <10,000.

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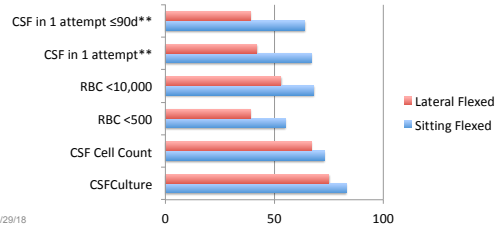
Lumbar puncture-3
Results

- 132 patients had complete data.
- Sitting flexed = 30; lateral flexed = 102.



Ultrasound guided LP-1

- Two prospective, randomized, controlled studies in pediatric EDs compared standard LP with bedside ultrasound guided LP
- Enrolled
  - Study 1: N = 128.
  - Study 2: N = 43.
- "Successful LP"
  - Study 1: Some CSF + RBC < 1000.
  - Study 2: 1.5 cc + RBC < 10,000.

Ultrasound guided LP-2

- Ultrasound Technique
  - Study 1: Optimal intraspinal location, depth to thecal sac.
  - Study 2: Interspace with greatest amount of CSF, maximum safe depth.
- Success Rates (US vs standard LP)
  - Study 1: 75% vs 44%. (Boston Children's + CHOP)
  - Study 2: 100% vs 82% (Dell Children's)
- Ann Emerg Med 2017;69:610. Acad Emerg Med 2017;24:6

Article 7

Comparison of peripheral and central capillary refill time in febrile children presenting to a paediatric ED and its utility in identifying children with serious bacterial infection

- De Vos-Kerkhof E, Krecinic T, Vergouwe Y, et al.
- Erasmus MC-Sophia Children's Hospital, Rotterdam.
- Arch Dis Child 2017;102:17-21

Capillary refill time-2
Methods-1

- Prospective, observational study.
- Tertiary children's hospital ED.
- Inclusion
  - Age 1 month to 16 years.
  - Temperature ≥ 38.5°C (rectal in infants; auricular in older children).
- Exclusion
  - Significant underlying comorbidity.

Capillary refill time-3
Methods-2

- Capillary refill time (CRT) = time from release until return of skin color.
  - Fingertip/nail bed = peripheral (pCRT)
  - Sternum = central (cCRT)
- CRT Categories
  - Normal = ≤ 2 sec.
  - Prolonged = >2 - ≤ 4 sec.
  - Severely prolonged = > 4 sec.

Capillary refill time-4
Methods-3

- Serious Bacterial Infection
  - E.g. sepsis, bacteremia, meningitis, pneumonia, UTI, bone and joint infections.
  - Final diagnosis extracted from final medical records.
- Analysis
  - pCRT and cCRT agreement.
  - Predictive value of any combination of CRT for SBI.

Capillary refill time-5
Results-1

- N = 1193.
- Age (median, IQR) = 1.67 yr (0.83-3.70)
- SBI in 138/1193 (11.6%)
  - Pneumonia = 5.5%.
  - UTI = 3.4%.
  - Sepsis/meningitis = 0.5%.
  - Other = 2.2%)

Capillary refill time-6
Results-2

	pCRT			
	Normal	Prolonged	Severe	Total
cCRT				
Normal	1026	110	2	1138
Prolonged	14	34	6	54
Severe	0	0	1	1
Total	1040	144	9	1193

Capillary refill time-7
Results-3

- Intermethod agreement (kappa) between pCRT and cCRT
  - Overall: 0.35 = fair.
  - SBI absent = 0.36 = fair.
  - SBI present = 0.24 = fair.
- No association with temperature or age.
- Odds ratio for SBI
  - pCRT = 1.10 (95% CI = 0.65-1.84)
  - cCRT = 0.43 (95% CI = 0.13-1.39)

Capillary refill time-8
Conclusion

- The diagnostic performance of an abnormal CRT [alone] for the presence of SBI in children is poor.

Extras

Recognition of sepsis in children-1

- The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) Clinical criteria for "suspicion of sepsis."
  - Clinical criteria for "suspicion of sepsis."
  - Rapid screening with a scoring system using RR, mental status, sBP.
  - Based on data from 1.3 million adult only patient encounters.
  - JAMA 2016;315:801

Recognition of sepsis in children-2

- There is no Sepsis-3 for children.
- Acad Emerg Med 2015;22:1298 (CHOP, Northwestern, Univ of Chicago)
  - 19,500 pediatric ED visits for fever or hypothermia.
  - Prevalence of severe sepsis was 0.45%.
  - (+) Likelihood ratio
    - Algorithm = 5.6.
    - Physician judgment = 148.79.
    - Sequential method = 200.8.

Article 6

Dry care versus antiseptics for umbilical cord care: A cluster randomized trial

- Gras-Le Guen C, Caille A, Launay E. et al.
- Universities of Nantes, Tours, Angers, Poitiers, Brest, Rennes.
- Pediatrics 2017;139:e20161857

Umbilical cord care-2 Methods-1

- Noninferiority, cluster-randomized, 2-period crossover and unmasked study.
- Six university hospitals western France.
- Inclusion
  - GA > 36 weeks.
  - Live birth.
- Exclusion
  - Malformation or early admission to NICU

Umbilical cord care-3
Methods-2

- Antiseptic Cord Care
  - 1-3 daily applications of antiseptic solution (benzyl alcohol, benzalkonium chloride, chlorhexidine, 70% alcohol).
- Dry Care
  - Soap and water cleaning and drying twice daily.

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Umbilical cord care-4
Methods-3

- Outcomes
  - Omphalitis
    - 1 or more: purulent or malodorous discharge, periumbilical erythema, edema, or tenderness.
  - Time to cord separation.
  - Parental dissatisfaction.
- Sample size to achieve a 90% power to detect a 2.5% difference.

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Umbilical cord care-5
Results

- N = 8120.
- Omphalitis
  - Dry: 3/3899 (0.08%).
  - Antiseptic: 0/4221.
- Time to Separation
  - Dry: 10 days.
  - Antiseptic: 11 days.
- Parent dissatisfaction: none

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Umbilical cord care-6
Conclusions

- Dry umbilical cord care is not inferior in preventing omphalitis to antiseptic cord care
- There were no differences between the groups in parent dissatisfaction or neonatal infection rates.
- Results are only applicable to high-income/ developed countries.

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Extras

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Omphalitis in developing countries

- Pakistan
  - 48 per 1000 live births.
- Rural Bangladesh
  - 4.2 to 155.7 per 1000 live births depending on infection severity.
- Recommended Cord Care
  - 4% chlorhexidine to umbilical stump within 24 hours after birth.
- Pediatrics 2016;138:e20162149.

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Article 5

Prevalence of concomitant bacterial meningitis in neonates with febrile urinary tract infection

- Wallace SS, Brown DN, Cruz AT.
- Texas Children's Hospital
- J Pediatr 2017;184:199-203.

Meningitis in UTI-2
Methods-1

- Retrospective cross-sectional study from 2005-2013.
- Neonates presenting to ED.
- Inclusion
  - Age < 30 days.
  - Fever > 38C rectally or by report.
  - UTI
  - CSF obtained.

Meningitis in UTI-3
Methods-2

- "UTI"
  - Urine via suprapubic aspiration of catheterization.
  - > 50,000 cfu/ml of single pathogen, or
  - > 10,000 cfu/ml + LE (+)/>5 wbc/hpf.
- Bacterial Meningitis
  - Any bacterial growth on CSF.
  - CSF pleocytosis (>20 WBC/mm^3) in antibiotic pretreatment with (-) viral studies.

Meningitis in UTI-4
Results-1

- N = 236.
- Male = 80%, of whom 73% were uncircumcised.
- 12% had GU tract abnormalities; 25% had VU reflux.
- LE (+) in 99%.
- UTI pathogens: E. coli = 86.9%, Klebsiella = 4.2%, other GNR = 5.5%, Enterococcus = 2.5%.

Meningitis in UTI-5
Results-2

- 6% had pretreatment with antibiotics.
- Bacteremia present in 9.7%.
- There were no cases of definite bacterial meningitis.
- 2 babies, both pretreated, had bloody CSF, looked well, but were treated with 7-10 days of antibiotics.
- 3 babies had viral meningitis/ meningoencephalitis: EV = 2, HSV = 1.

Meningitis in UTI-6
Conclusions

- Concomitant bacterial meningitis occurs "uncommonly" in neonates with febrile UTI.

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Ditto

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UTI in febrile neonates
Pediatr Infect Dis J 2014;33:342
Maimonides Medical Center

- 651/670 febrile neonates < 30 days of age had urine cultures obtained.
- 100 (15%) had UTI.
- In babies with UTI, there were no cases of bacterial meningitis.

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Age-related risk of co-existing meningitis in children with UTI
PLoS One 2011;6:e26579
Royal Children's Hospital, Melbourne

- 2/163 neonates < 28 days had co-existing meningitis with UTI.
  - Staphylococcus aureus + E. coli.
- Both had clinical meningitis on admission.
- No cases of co-existing meningitis in 585 children 1 mo. to 16 yr. of age.

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UTI concordance with (+) blood and CSF in NICU.
J Perinatol 2013;33:301
Duke University + Pediatrix

- 1162 episodes of UTI managed in NICU
- 976/1162 (84%) had blood cultures; 127/976 (13%) grew concordant organism.
- 77/1162 (7%) had CSF obtained
- 2 cases of concordant bacterial meningitis.

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Extras

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Corrections for leukocytes and percent of neutrophils do not match observations in blood-contaminated cerebrospinal fluid and have no value over uncorrected cells for diagnosis

- Bonsu BK, Harper MB
- Children's Hospitals, Boston and Columbus
- *Pediatr Infect Dis J* 2006;25:8-11

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Traumatic tap-2 Methods-1

- Retrospective study: 1993-2003
- Age: 1month - 18 years
- "Traumatic" = RBC ≥ 500 cells/µL
- "Normal" = (-) CSF cultures/PCR and no: head injury, CNS disease, sepsis, meningitis/encephalitis
- Excluded: CSF blood with CSF WBC > 20/µL (minimize aseptic meningitis)

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Traumatic tap-3 Methods-2

- "Predicted CSF-WBC" = CSF RBC/500
  - Peripheral WBC/RBC ≅ 1/500
- Excluded CSF-RBC > 10,000/µL (based on exclusion of CSF-WBC > 20/µL)
- Sensitivity analysis for CSF RBC > 10,000/µL as fail-safe
- Strength of correlation (R^2)
  - 0 = relationship due to chance only
  - 1 = rule perfectly predictive

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Traumatic tap-4 Methods-3

- Determined "incremental value for diagnosis" of bacterial meningitis of corrected over uncorrected CSF- WBC
  - "Corrected" = observed - predicted
- Calculated receiver operator characteristic curve (AUC)
  - AUC = 0.5 means test (correction) has no value for diagnosis

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Traumatic tap-5 Results-1

- 16,820 CSF specimens
- 2,907/16,820 (17%) had CSF-RBC > 500/µL
- 682/2907 met study criteria
- Strength of correlation (R^2) between observed and predicted WBC and %PMN was a weak 0.27 (0.25-0.28) at every level CSF-RBC

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Traumatic tap-6 Results-2

- In 2907 cases of CSF-RBC > 500 µL, 7 cases of bacterial meningitis
- Corrected CSF-WBC and %PMN (= observed - predicted) added no significant incremental value over the uncorrected CSF-WBC in predicting bacterial meningitis (AUC ≅ 0.8)

3/29/18

Traumatic tap-7 Conclusion

- Predicted CSF-WBC correlates poorly with observed CSF-WBC
- Correcting CSF-WBC adds no incremental benefit in diagnosis of bacterial meningitis
- In traumatic CSF, uncorrected CSF-WBC and %PMN should be used and compared to published norms

3/29/18

Effect of antibiotic pretreatment on cerebrospinal fluid profiles of children with bacterial meningitis

- Nigrovic LE, Malley R, Maclas CG, et al.
- American Academy of Pediatrics, Pediatric Emergency Collaborative Research Committee
- *Pediatrics 2008;122:726-730*

3/29/18

Pretreatment in meningitis-2
Methods

- Retrospective cohort study
- 20 EDs in pediatric centers in US
- All cases of bacterial meningitis 1/01-7/04
- Ages: 1 month-18 years
- "Pretreatment" = antibiotics ≤ 72 hours of LP

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Pretreatment in meningitis-3
Results-1

- 245 patients with bacterial meningitis
  - [= 3.5 cases per ED per year]
- 85/245 (35%) had pretreatment
  - 20/85 (24%) had PO antibiotics
  - 59/85 (69%) had parenteral antibiotics
  - 6/85 (7%) had PO + parenteral antibiotics

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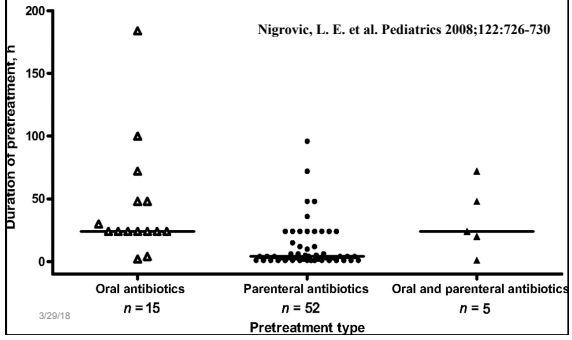
Pretreatment in meningitis-4
Results-2



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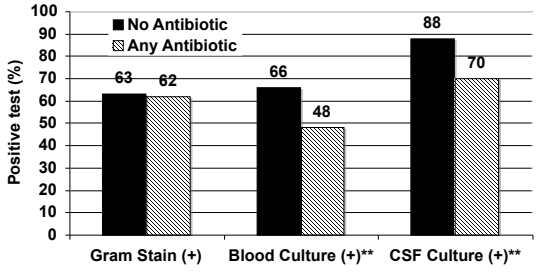
Pretreatment in meningitis-5
Results-3



-35% had isolation of pathogen in BC alone

Pretreatment in meningitis-6
Results-4

- CSF WBC or CSF ANC not association with pretreatment
- Greater the duration of antibiotics, the greater the effect on CSF glucose and CSF protein

Pretreatment in meningitis-7
Conclusions

- Bacterial meningitis is rare
- Pretreatment with antibiotics in bacterial meningitis is common (35%)
- Pretreatment does not affect rate of positive gram stain nor CSF WBC or CSF ANC counts
- The longer the duration of antibiotics, the greater the modification of CSF glucose and CSF protein
- Most pretreated patients still have pathogen recovered from blood or CSF

Article 4

What is the risk of a repeat reaction to amoxicillin or a cephalosporin in children with a history of non-immediate reaction to amoxicillin?

- Grinlington L, Cranswick N, Gwee A.
- Royal Children's Hospital, Melbourne
- Arch Dis Children 2017;102:285

Repeat ABX reaction-2
Methods

- Systematic literature review (1946-2016), English-language.
- 282 articles found.
- 5 relevant publications
  - Prospective
  - Children
  - History of non-immediate reaction to amoxicillin or cephalosporin.
  - Oral rechallenge.

Repeat ABX reaction-3
Background

- "Immediate hypersensitivity reactions"
  - IgE mediated.
  - Reaction to ß-lactam core or side chain.
  - Symptoms usually < 1 hour.
- Non-immediate reactions (NIR)
  - T-cell recognition of the whole molecule.
  - Non-IgE mediated.
  - Onset hours to days.
  - Often occur in context of viral infection.

Repeat ABX reaction-4
Results

- NIR to amoxicillin: 6.8%-12.4% of pediatric population.
- 42/542 (7.7%, range 0% to 9.9%) had repeat reaction to oral rechallenge.
  - Patch or intradermal testing did not predict.
  - 35/42 (83.3%) had maculopapular rash or urticaria.
  - 7/42 (16.6%) had urticaria/angioedema.
  - No child had anaphylaxis or required hospitalization.

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Repeat ABX reaction-5
Conclusions

- In children with a history of NIR to amoxicillin, the risk of a repeat reaction is low (0% to 7.7%)
- Angioedema in 1%.
- Data for children with initial reaction of angioedema limited (caution!)
- Anaphylaxis does not occur.
- Risk of cephalosporin cross-reactivity appears to be rare, but data are scanty.

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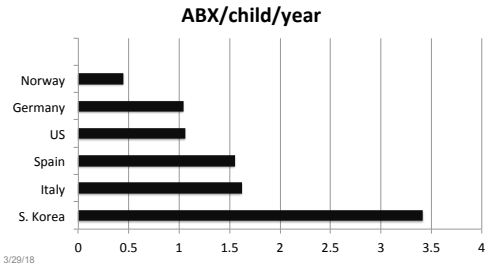
Extras

3/29/18

Antibiotic use in children 0-2 years in 6 countries
J Pediatr 2017;182:239



3/29/18

Simplified gentamicin dosing in neonates
J Perinatol 2016;36:660

- Prospective, randomized study.
- 96 neonates. GA 24-41 weeks.
- Extended interval (EI) dosing (5 mg/kg/ 36h) compared to traditional dosing.
  - Same peak level. Same areas under the curve. Risk of trough levels > 2 mcg/ml reduced from 12% to 4% in prematures and 39% to 0% in term babies.

3/29/18

RISK TOLERANCE

3/29/18

Risks of daily life
Odds of death/person-year
JAMA 1980;244:1226

Motorcycling	1 in 50
Smoking 20/day	1 in 200
Pregnancy	1 in 4,350
Rock climbing	1 in 7,150
Leukemia	1 in 12,500
Earthquake (Calif.)	1 in 588,000
Hit by meteorite	1 in 100 billion

3/29/18

Scientists investigate suspected meteorite death in Tamil Nadu
Reuters 2/8/16

- Bus driver at a local college was standing on a patch of grass near the cafeteria when he was killed. A dark blue stone resembling a diamond was found at the scene.
- If confirmed, it would be the first recorded death from space rock since 1825 according to a list kept by International Comet Quarterly

3/29/18

Risk perception factors-1
Harvard Center for Risk Analysis

- People are more afraid of risk that is new.
- People are more afraid of risk that is human-made than risk that is natural.
- People are more afraid of risk that is imposed on them than on risk they choose to take.

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Risk perception factors-2

- People are less afraid of risk if the risk also confers some benefits they want.
- People are more afraid of risk that can kill them in awful ways.
- People are more afraid of risk they can't control.
- People are more afraid of risk when uncertainty is high.
- People are more afraid of risk that comes from a source they don't trust.

3/29/18

Weighing of risk in medicine

- Intolerance of risk with outcomes that are uncontrollable, unpreventable, delayed, dread, fatal, catastrophic.
- Ambiguity avoidance: acceptance of higher level of risk if firm risk estimate.
- Hindsight bias.
- *Innate threshold difference not correlated with level of medical training.*
- *Science* 1987;236:280. *N Engl J Med* 1989;320:1489

3/29/18

Variability in Probability Expressions among Physicians

- "Certain"
  - –Mean = 95%; range = 70%-100%
- "Probable"
  - –Mean = 71%; range = 30%-95%
- "Likely"
  - –Mean = 68%; range = 20%-95%
- *N Engl J Med 1980;302:411. N Engl J Med 1986;315:740*

3/29/18

Article 3

Duration of antibiotic therapy for community-acquired pneumonia : A multicenter randomized clinical trial

- Uranga A, España PP, Bilbao A, et al.
- 4 teaching hospitals in Basque Country, Spain.
- JAMA Intern Med 2016;176:1257-1265.

Duration of ABX in CAP-2
Methods-1

- Multicenter, prospective, noninferiority, randomized clinical trial in adults.
- Inclusion
  - Hospitalized with community acquired pneumonia (CAP).
  - CAP = Pulmonary infiltrate on CXR plus 1 symptom of pneumonia: fever, cough, dyspnea, chest pain.

Duration of ABX in CAP-3
Methods-2

- Exclusion
  - Immunodeficiency, nursing home, recent hospital discharge or antibiotics, chest tube, extra-pulmonary infection.
- Random assignment
  - Study group: antibiotics for 5 days; stop if temperature normal x 48 hours and clinically stable.
  - Control group: determined by MD.
- Antibiotics: guidelines (macrolide +/- ß-lactam or fluoroquinolones).

Duration of ABX in CAP-4
Methods-3

- Laboratory testing
  - An etiologic diagnosis was made whenever the reuslts of urinary antigen testing for Legionella pneumophila typ 1 or S. pneumoniae, serological tests, or blood or sputum culture were positive.

Duration of ABX in CAP-5
Methods-4

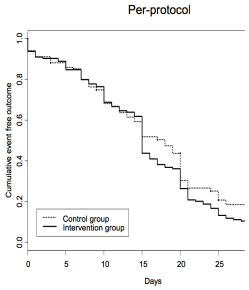
- Outcomes
  - 1°: Clinical success at days 10 and 30: resolution/improvement in signs/symptoms related pneumonia (patient questionnaire)
  - 2°: Time until clinical improvement, return to normal activity, pneumonia resolution on CXR day 30, recurrence, hospital readmission, length of hospital stay.
- Sample size: 80% power to detect symptom score change of 3/18 points.

Duration of ABX in CAP-6
Results-1

- N = 312.
- Mean age 65 years.
- Organisms (63/312): Pneumococcus (80%); Legionella (5%); Mycoplasma (3%); Chlamydia (3%); viral (3%).
- Antibiotics: similar in both groups.
- Duration (median, IQR): control = 10 days (10-11); study = 5 days (5-6.5).

Duration of ABX in CAP-7
Results-2

- Clinical success day 10
  - Control = 48.6%.
  - Study = 56.3%.
- Clinical success day 30
  - Control = 88.6%.
  - Study = 91.9%.



Duration of ABX in CAP-8
Results-3

- Secondary Outcomes
  - No difference in: time until clinical improvement, return to normal activity, radiological resolution, in-hospital and 30-day mortality, in-hospital complications, recurrences, and length of hospital stay.
  - Readmission by day 30 was significantly more common in the control group (6.6% vs 1.1%)

Duration of ABX in CAP-9
Conclusions

- Shorter duration of antibiotics based on clinical stability criteria can be safely implemented in hospitalized adults with community acquired pneumonia.
- Welcome to the era of "personalized antibiotic therapy" = individualizing duration of antibiotics using clinical stability criteria and biomarkers.

Extras

Three day versus five day treatment with amoxicillin for non-severe pneumonia in young children: a multicentre randomised controlled trial

- ISCAP Study Group
  - India (7 clinical sites), WHO, McMaster
- *BMJ* 2004;328:791-799)

Duration of antibiotics
Methods-1

- Double blind, placebo controlled, randomized trial
- Outpatients in 7 referral hospitals
- Children 2-59 months
- Inclusion
  - Respiratory symptoms (cough, rapid breathing)
  - Tachypnea: RR ≥ 50/min (< 12 m/o) or ≥ 40/min (≥ 12 m/o) despite antipyretics (if fever) and beta 2-agonist (if wheezing)
  - Exclusion: "severe" pneumonia (cyanosis, "toxic")

Duration of antibiotics
Methods-2

- RSV swabs performed on all
- Amoxicillin 125 mg tid x 5d vs. amoxicillin x 3 d + placebo x 2d
- Follow-up: 3, 5, 12, 14 days
- "Failure" = Deterioration to "severe," tachypnea on day 3, SpO2 < 90% on day 3, "relapse" after day 5

Duration of antibiotics
Results

- 2188 patients recruited and randomized
- Loss to follow-up 5.4% by day 5 (= failure)
- Compliance > 90%
- 23% RSV (+) equal in both groups
- 95% cure rates in both groups

Duration of antibiotics
Conclusions

- In ambulatory pneumonia for which antibiotic treatment is chosen, 3 days of therapy is usually sufficient
- Amoxicillin remains the antibiotic of choice in non-severe childhood (<5 yr) pneumonia requiring therapy

Duration of antibiotics (part 2)

- "Clinical efficacy of 3 days vs 5 days of oral amoxicillin for treatment of childhood pneumonia"
  - Pakistan Multicentre Amoxicillin Short Course Therapy (MASCOT) pneumonia study group
- Same study design
- 45 mg/kg/day amoxicillin divided tid
- 2000 children
- Same result
- *Lancet* 2002;360:835-841

Laboratory in pneumonia-1

- WBC and differential: "tie-breaker" only.
- Blood culture: low yield.
- CRP > 4 mg/dL weakly predicts a "presumptive bacterial" etiology (OR = 1.2-5.5).
  - *Pediatr Infect Dis J* 2008;27:95
- Urine antigen detection: only available for few pathogens and often falsely negative.

Laboratory in pneumonia

- Pneumococcal immune complexes: don't hold your breath.
- Multiplex PCR
  - Extremely sensitive
  - May identify carrier state.
  - Documents what's in the nose but not in the lungs.
- *The cause of pneumonia cannot be determined with confidence by laboratory means.*

Overcall in Interpreting Chest Radiographs in Febrile Infants

- 287 chest radiographs in infants of 3-24 months
- Compared readings of treating pediatrician with "blind" radiologists
- Films read as abnormal by treating physician were read as abnormal by blind radiologist only 54% of time
- Kappa = 0.462
- *Pediatrics* 1992;90:11

Physician assessment of the likelihood of pneumonia in a Pediatric Emergency Department

- Neuman MI, Scully KJ, Kim D et al.
- Boston Children's Hospital
- *Pediatr Emer Care 2010;26:817-822*

Assessment of pneumonia-2 Methods-1

- Prospective observation study in urban ED with 56,000 yearly visits.
- Inclusion criteria
  - Age < 22 years
  - CXR obtained for "suspicion of pneumonia"
- Exclusion criteria
  - CXR for any other purpose.
  - Chronic pulmonary or immune illnesses

Assessment of pneumonia-3 Methods-2

- Ordering physician completed a questionnaire before CXR obtained
  - Indicate probability of pneumonia based on history, physical examination and lab (if ordered): 5%, 5%-10%, 11%-20%, 21%-50%, 51%-75%, 75%-100%.
  - Indicate reason for CXR: height of fever, duration of fever, duration of cough, abnormal lung exam, high WBC, or "other."
  - Record temperature, auscultation findings and respiratory rate.
- CXR classified as: pneumonia, negative, equivocal

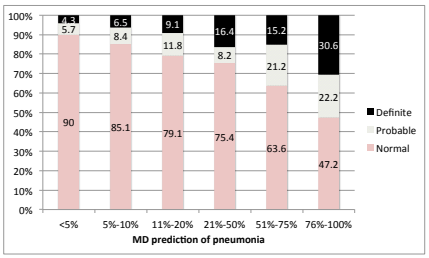
Assessment of pneumonia-4 Results-1

- 2071 patients enrolled in study.
- Median age 2.3 years (IQR = 0.8-5.2 y)
- Results of CXR
  - 7.1% definite pneumonia
  - 15.5% probable pneumonia
  - 77.4% negative
- 28% had antibiotics given in ED.
- 22% admitted to hospital

Assessment of pneumonia-5
Results-2

- Most common indications (not mutually exclusive) for ordering CXR () and % with definite/probable pneumonia
  - Duration of cough (32%): 17%.
  - Height of fever (31%): 17%.
  - Duration of fever (23%): 23%.
  - Abnormal lung exam (29%): 19%
    - Compelling findings in order: tachypnea, focal decreased breath sounds, retractions, rales

Assessment of pneumonia-6
Results-3



Assessment of pneumonia-7
Results-4

- Children < 2 years
  - Low risk of pneumonia (<5%) – actual pneumonia (definite/probable) = 8%.
  - High risk of pneumonia (>50%) – higher actual rate of pneumonia (definite/probable) =24%.
- Children > 10 years
  - Low risk of pneumonia – low actual rate of pneumonia (definite/probable)= (<5%.
  - High risk of pneumonia – high actual rate of pneumonia (definite/probable) = 45%.

Assessment of pneumonia-8
Conclusions

- Although there is often a poor correlation between individual physical findings and radiological pneumonia, MD prediction of pneumonia directly correlated with the results of the CXR.
- Predictive accuracy was directly related with the age of the patient.
- Clinical judgment remains THE important factor in the management of children with illness

Prospective evaluation of point-of-care ultrasonography for the diagnosis of pneumonia in children and young adults

- Shah VP, Tunik MG, Tsung JW.
- Departments of Emergency Medicine: Children's Hospital at Montefiore, Bronx; Bellevue Hospital Center, NYC
- *JAMA Pediatr 2013;167:110-125*

Ultrasound in pneumonia-2
Methods-1

- Prospective observational study.
- Inclusion: Age: birth – 21 years; clinical suspicion of community-acquired pneumonia (CAP) who required CXR.
- Exclusion: unstable; prior pneumonia.
- "Sonologists" = 15 ED MDs with 1-hour chest sonography (US) training session on system of Copetti *(Radiol Med 2008;113:190)*

Ultrasound in pneumonia-3
Methods-2

- Results of ED "sonologists'" interpretation of US compared to radiologists' interpretation of AP/lateral CXR.
  - "Equivocal" CXR = negative CXR
- Investigator-sonologists reviewed movie clips of all US studies.

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Ultrasound in pneumonia-4
Results

- 200 patients; median age 3 years.
- Prevalence radiological pneumonia = 18%
- Mean US time = 7 minutes
- US vs CXR (sonodensities > 1 cm)
  - Sensitivity = 86%; Specificity = 146
  - PPV = 86%; NPV = 97%
  - LR+ 28.2; LR- = 0.14

3/29/18

Ultrasound in pneumonia
Recent literature-1

- Pediatr Emerg Care 2017;33:62
  - In 69 children with clinical CAP, there was no difference in the diagnostic value of US or CXR for the diagnosis of pneumonia.
- Acad Emerg Med 2016;23:932
  - In 116 febrile events in children with sickle cell disease, US was highly accurate (+LR = 14.6, -LR = 0.14) in making the diagnosis of acute chest syndrome.

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Ultrasound in pneumonia
Recent literature-2

- Chest 2016;150:131
  - In 191 children suspected of CAP screened with US, there were no cases of missed radiological pneumonia.

3/29/18

Resolution of CXR in pneumonia-adults

- *New Engl J Med* 1975;293:798-801
  - Serial CXR in 72 patients with pneumococcal pneumonia
  - Consolidation disappeared in 8-10 weeks
- *Clin Infect Dis* 2007;45:983-991
  - Severe CAP in 288 patients
  - By 4 weeks, 53% had resolution of CXR abnormalities
  - CXR resolution not related to outcome

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Resolution of CXR in pneumonia-children

- *N Z Med J* 1998;111:315-317
  - 65 pediatric admissions for pneumonia
  - At 4-6 weeks, no child with clinical resolution had an abnormal CXR; no child with abnormal CXR was clinically normal
- *Pediatr Pulmonary* 2005;40:223-227
  - 196 children hospitalized for pneumonia
  - F/U CXR 3-7 weeks after admission
  - Findings on F/U CXR did not influence management

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Use of pulse oximetry to exclude pneumonia in children

- Tanen DA, Trocinski DR
- Naval Medical Center, San Diego
- *Am J Emerg Med* 2002;20:521-523

3/29/18

Pulse oximeter and pneumonia-2

- Methods
  - Retrospective chart review over 1 year
  - Children < 24 months with respiratory complaints presenting to ED
  - Pulse oximetry and chest x-ray performed
- Results
  - 807 met inclusion criteria
  - 78 cases of radiologic pneumonia

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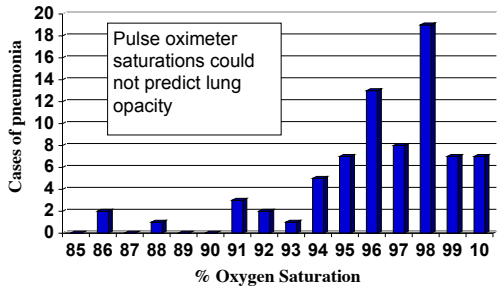
Pulse oximeter and pneumonia



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Comparative effectiveness of beta-lactam versus macrolide monotherapy in children with pneumonia diagnosed in the outpatient setting

- Ambroggio L, Test M, Metlay JP, et al.
- Cincinnati Children's Hospital, Geisinger Health System (GHS)
- Pediatr Infect Dis J 2015;34:839

3/29/18

Antibiotics for pneumonia-2
Methods-1

- Retrospective cohort study: 2008-2010.
- Inclusion
  - Patient within GHS.
  - Age 1-18 years.
  - Clinical diagnosis of community acquired pneumonia (CAP) in outpatient setting.
- Exclusion
  - Immunocompromised.
  - Chronic medical condition (not asthma).
  - Did not receive antibiotics after 1st visit.

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Antibiotics for pneumonia-3
Methods-2

- Compared any beta-lactam antibiotic vs any macrolide if given as monotherapy.
- Outcome measure
  - Treatment failure = hospital admission < 14 days or repeat visit + change in antibiotic < 7 days.
- Statistical analysis
  - Extensive

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Antibiotics for pneumonia-4
Results

- 1164 children enrolled
- Matched cohort with 582 in each group.
- Age
  - 1-5 years = 47%.
  - 6-18 years = 53%.
- Antibiotics by age
  - 1-5 yr: beta-lactam 62%; macrolide 38%.
  - 6-18 yr: beta-lactam 38%; macrolide 62%.

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Antibiotics for pneumonia-5
Conclusions

- In children with ambulatory clinical pneumonia who require antibiotics, the choice of antibiotic is [probably] irrelevant.
- There is a trend (not statistically significant) among older children for a lower risk of failure if given a macrolide.
- Since the cause of ambulatory pneumonia is not [almost never] known, the decision to give an antibiotic and the choice of antibiotic remain "an art."

3/29/18

Article 2

3/29/18

Management and outcomes of previously healthy, full-term febrile infants ages 7 to 90 days

- Greenhow TL, Hung, YY, Pantell RH.
- Kaiser Permanente and University of California, San Francisco
- Pediatrics 2016;138:e20160270

3/29/18

Management of infant fever-2
Methods-1

- Retrospective cohort study.
- Data from Kaiser Permanente of Northern California (3.2 M members).
- Inclusion
  - Age 7-90 days.
  - Born between 7/1/10 and 6/30/13
  - Full term and previously healthy.
  - T (R or Ax) ≥ 38°C.
  - Evaluated in a medical facility.

3/29/18

Management of infant fever-3
Methods-2

- Data on age, gender, race/ethnicity, circumcision, laboratory studies ordered, ill appearance, antibiotic prescriptions, height and duration of fever, recent immunizations, and final diagnosis, and disposition collected.
- All clinic notes for each child for the next month reviewed.
- Comparisons involving categorical variables performed and analyzed.

3/29/18

Management of infant fever-4
Results-1

- During 3 years, 96,156 full-term infants were born.
- 1380 (1.4%) received care for fever.
- 195 (14%) had bacterial infections: UTI = 13.2%, bacteremia = 2.6%, meningitis = 0.3%.
- Bacterial infections by age: 7-28 d = 18.8%, 29-60 d = 13.9%, 61-90 d = 10.8%.

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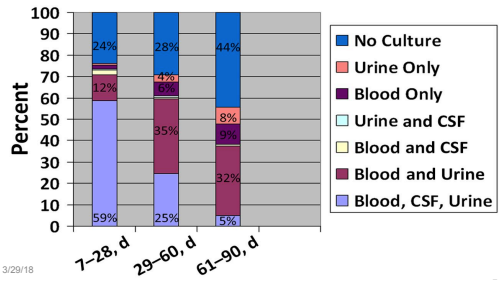
Management of infant fever-5
Results-2

- 68% had at least 1 culture obtained



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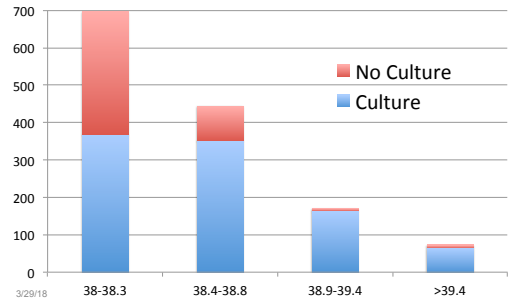
Management of infant fever-6
Temperature and cultures taken



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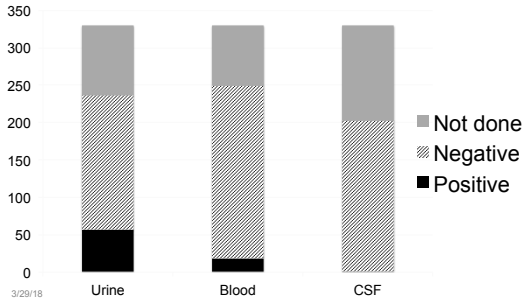
Management of infant fever-7
Results of cultures age 7-28 days



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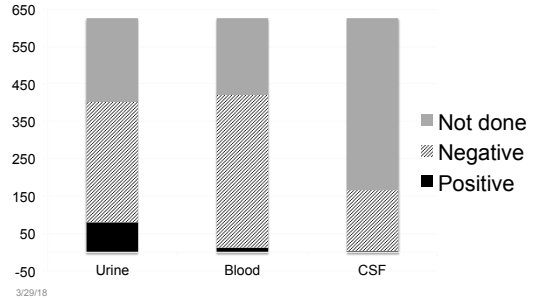
Management of infant fever-8
Results of cultures age 29-60 days



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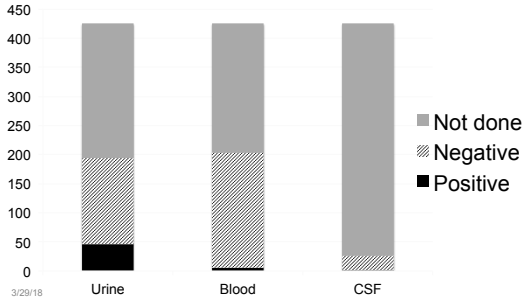
Management of infant fever-9
Results of cultures age 61-90 days



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Management of infant fever-10
Results-7

- Reasons cited for not obtained cultures in 429 febrile infants
  - Other diagnosis (e.g. AOM, pneumonia)
  - Immunizations recently given.
  - URI/bronchiolitis symptoms.
  - Sick contacts appeared well.
  - Did not believe reported home temperature
  - Parents declined.

3/29/18

Management of infant fever-11
Results-8

- 95% were non-ill appearing.
- Ill appearing babies had more cultures.
- "Ill appearing" predicted serious bacterial infection (SBI) in infants 7-28 days but not in older infants.
- Of 442/1380 (32%) who had no cultures obtained, 5 (1%) had subsequent UTI. There were no cases of subsequent bacteremia or meningitis.

3/29/18

Management of infant fever-12
Conclusions

- Physicians are using selective strategies in deciding which febrile infants will have cultures obtained.
- Although there is a low incidence of truly serious bacterial infections in infants (bacteremia = 0.4/1000 LB; meningitis = 0.04/1000 LB) the absence of delayed recognition of SBI is noteworthy.

3/29/18

- Welcome to the era of "personalized medical care" = individualizing evaluation and management using clinical findings, selected ancillary testing, and sharing of uncertainty with families.

3/29/18

Editorial-1
Johns Hopkins University
Pediatrics 2016;138:e20162085

- Why the disconnect between office practice and academic centers?
- Are office MDs superior clinicians or do they just see fewer febrile infants?

3/29/18

Editorial-1
Johns Hopkins University
Pediatrics 2016;138:e20162085

- Why the disconnect between office practice and academic centers?
- Are office MDs superior clinicians or do they just see fewer febrile infants?
- "A disconcerting reality of common practice is what seems [to us] to be a dismissal by many practitioners of established scientific evidence."

3/29/18

Editorial-2

- All of the reasons given for not culturing "have been investigated previously and have been shown to *not excuse or eliminate the need* for further investigation of cause of fever in your infants."
- Several studies have shown "that clinical impressions are not *entirely* reliable."

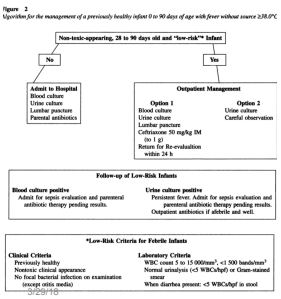
Editorial-3

- "It is good that the occurrence of serious bacterial illness in young febrile infants is low."
- "Often our management practices are affected by commonalities of practice, which might be influenced by patient conveniences, personal habits, or other experiential biases. To that end, we must always make the effort to use *sound scientific evidence* as a basis for our standard practice of medicine."

Extras

Practice guideline for management of infants and children with fever without source

Pediatrics 1993;92:1 • Ann Emerg Med 1993;22:1198



- Larry Baraff
- David Schriger
- James Bass
- Gary Fleisher
- Jerome Klein
- George McCracken
- Keith Powell

Management and outcomes of care of fever in early infancy

- Pantell RH, Newman TB, Bernzweig J, et al
- University of California, San Francisco
- Conducted by the Pediatric Research in Office Settings (PROS) practice-based research network of the AAP
- *JAMA* 2004;291:1203-1212

Fever in infancy-2
Methods-1

- Eligible infants
  - Age ≤ 3 months
  - T ≥ 38°C at home or in office
    - Maximal rectal temperature taken in office or reported by parent in past 24h; if axillary temp, add 0.5°C
  - No major co-morbidities
- Prospective cohort study design
- 2/28/95-4/25/98

Fever in infancy-3
Results-1

- 573 practitioners submitted data
- 3066 consecutive infants enrolled
- 1975/3066 (64%) ambulatory management
- Predictors of laboratory testing (WBC, BC)
  - Age ≤ 30 days
  - "Very ill" vs "well"
  - Received care after hours
- 1666/3066 (54%) had urine testing

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Fever in infancy-4
PROS practitioner adherence to guidelines

Age/Appearance	Recommendations	Guideline followed (%)
< 31 days	Sepsis w/u, hospitalize, antibiotics	45.7
31-90 days + mod/very ill	Sepsis w/u, hospitalize, antibiotics	35.8
31-90 days + well/mildly ill	WBC, UA	41.6

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Fever in infancy-5
Results-3

- Serious infections in 3066 febrile infants
  - Bacteremia - 54 (1.8%)
  - Bacterial meningitis - 14 (0.5%)
    - 5/14 bacteremic
  - UTI - 167 (5.4%)
    - 18/167 bacteremic
  - Practitioners treated 61 of 63 infants with bacteremia or meningitis on the initial visit

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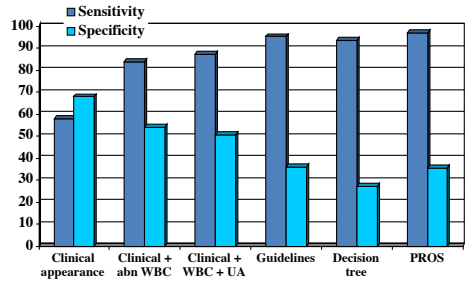
Fever in infancy-6
Performance of prediction models



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Fever in infancy-7
Conclusions (my)

- Office practitioners are practiced at managing uncertainty.
- Office practitioners order fewer tests than guidelines [generated in academic centers] recommend, yet the "miss" rate of infants with bacteremia or meningitis is very low.
- Parent partnering and the ability to follow-up patients (return visits, telephone) constitute a safety net and allow for "masterful inactivity."

3/29/18

What is a fever in newborns and young infants?

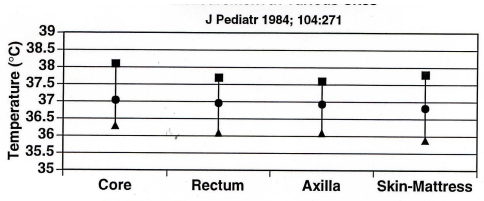
Temperature measurement in term and preterm neonates

- Mayfield SR, Bhatia J, Nakamura KT, et al
- University of Iowa
- *J Pediatr* 1984;104:271-275

Temperature in newborns-2
Methods

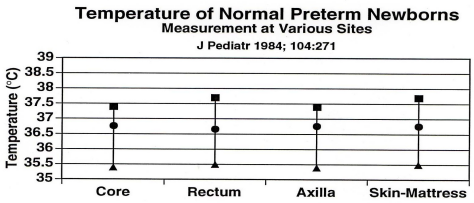
- 99 term (≥ 37 wks) and 44 preterm, "not ill" infants
- Age < 28 days
- "Core" = 5 cm rectal with thermistor probe
- Glass thermometers
  - Rectal = 2 cm depth
  - Axillary = right axilla
  - Skin-mattress

Temperature in newborns-3



	High	Low	Mean
Core	38.1	36.3	37.04
Rectum	37.7	36.1	36.96

Temperature in newborns-4



	High	Low	Mean
Core	37.4	35.4	36.76
Rectum	37.7	35.5	36.66
Axilla	37.4	35.4	36.76
Skin-Mattress	37.7	35.5	36.76

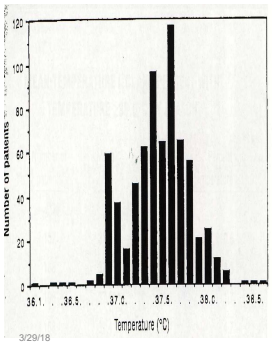
What is fever?
Normal temperature in infants less than 3 months old

- Herzog LW, Coyne LR
- Boston Children's Hospital
- *Clin Pediatr* 1993;32:142-146

What is fever?-2
Methods

- Retrospective chart review
- Infants < 3 months old
- Well-baby clinic
- 8:30 am - 8:30 pm
- Rectal temperatures
- Undressed
- All ill children excluded

What is fever?-3



- 6.5% had T ≥ 38°C.
- When retaken, 90% with T ≥ 38°C had T < 38°C.
- 1 child with T ≥ 38°C returned in 48 hours with AOM.

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What is a fever in a neonate or young infant?

- Arbitrary
- T ≥ 38.3°C (101°F) = fever
- 37.8°C (100°F) - 38.3°C = ?
- When in doubt? Measure twice!

Article 1

3/29/18

Shortened antimicrobial treatment for acute otitis media in young children

- Hoberman A, Paradise JL, Rockette HE, et al.
- Pittsburgh Children's Hospital
- N Engl J Med 2016;375:2446-2456

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Antibiotics in AOM-2 Methods-1

- Prospective, randomized, non-inferiority trial.
- Pittsburgh Children's Hospital and affiliated pediatric practices.
- Inclusion
  - Age 6-23 months.
  - ≥ 2 doses of PCV.
  - Otitis media.

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Antibiotics in AOM-3 Methods-2

- "Otitis media"
  - Onset < 48 hours.
  - Parents rated severity ≥ 3 on 7 item AOM Severity of Symptoms scale (AOM-SOS).
  - Middle ear effusion.
  - Moderate/marked TM bulging, *or* slight bulging + otalgia and marked erythema.

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Antibiotics in AOM-4
Methods-3

- AOM-SOS
  - Tugging of ears.
  - Crying.
  - Irritability.
  - Difficulty sleeping.
  - Diminished activity.
  - Diminished appetite.
  - Fever
- None = 0. A little = 1. A lot = 2

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Antibiotics in AOM-5
Methods-4

- Excluded
  - TM perforation.
  - Allergic to amoxicillin.
  - Antibiotics < 96 hours.
- Randomization
  - Amoxicillin-clavulanate @ 90 mg/kg/day x 10 days.
  - Amoxicillin-clavulanate x 5 days + placebo x 5 days.

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Antibiotics in AOM-6
Methods-5

- Follow-up
  - Telephone on days 4, 5, and 6.
  - End-of-treatment office visit.
  - Parents recorded AOM-SOS daily.
  - Office visit every 6 weeks.
- "Clinical Failure"
  - Worsening of symptoms.
  - Worsening otoscopic signs of infection
  - Incomplete otoscopic resolution at end-of-treatment.

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Antibiotics in AOM-7
Results-1

- N = 520.
- Clinical failure
  - 5-day = 34%. 10 day = 16%.
  - 17% difference (unrounded data) had 95% CI of 9% to 25%.
  - Not reported: the proportion of symptomatic failure vs otoscopic failure.
- Clinical failure greater with "probably severe" illness (based only on pain and fever history).

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Antibiotics in AOM-8
Results-2

- Clinical failure not linked to AOM-SOS, degree of TM bulging, but ± bilaterality.
- No difference in risk of recurrence or in risk of middle ear effusion.
- No difference in nasal colonization with resistant strains of S. pneumoniae.
- Adverse events
  - Diarrhea: 10-day = 30%. 5-day = 29%.
  - Diaper rash: 10-day = 33%. 5-day = 34%.

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Conclusions

- In children 6-23 months of age, the treatment of AOM with 5-day therapy "afforded less-favorable short-term outcomes than treatment for 10 days."

3/29/18

Conclusions

- In children 6-23 months of age, the treatment of AOM with 5-day therapy "afforded less-favorable short-term outcomes than treatment for 10 days."
- [Number needed to treat (NNT) = 6.]
- [Unclear proportion of symptomatic vs otoscopic failure.]

Cultures of non-resolving AOM

- 3 tympanocentesis studies
- N= 244 (USA, France, S. Africa)
- Sterile fluid in 45%, 57% and 73% respectively.
- Of non-sterile fluid, up to 1/4 grew organisms susceptible to current antibiotic.
- *J Pediatr* 1981;98:537; *J Laryngol Otol* 2003;117:169; *J Laryngol Otol* 2003; 117:173

Extras

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 13, 2011 VOL. 364 NO. 2

Treatment of Acute Otitis Media in Children under 2 Years of Age

Alejandro Hoberman, M.D., Jack L. Paradise, M.D., Howard E. Rockette, Ph.D., Nader Shaikh, M.D., M.P.H., Ellen R. Wald, M.D., Diana H. Kearney, R.N., C.C.R.C., D. Kathleen Colborn, B.S., Marcia Kurs-Lasky, M.S., Sonika Bhatnagar, M.D., M.P.H., Mary Ann Haralam, C.R.N.P., Lisa M. Zoffel, C.R.N.P., Carly Jenkins, R.N., Marcia A. Pope, R.N., Tracy L. Balentine, R.N., and Karen A. Barbadora, M.T.

ABSTRACT

BACKGROUND

Recommendations vary regarding immediate antimicrobial treatment versus watchful waiting for children younger than 2 years of age with acute otitis media.

METHODS

We randomly assigned 291 children 6 to 23 months of age, with acute otitis media diagnosed with the use of stringent criteria, to receive amoxicillin–clavulanate or placebo for 10 days. We measured symptomatic response and rates of clinical failure.

From the Department of Pediatrics, University of Pittsburgh School of Medicine, Children's Hospital of Pittsburgh of the University of Pittsburgh Medical Center (A.H., J.L.P., N.S., E.R.W., D.H.K., D.K.C., S.B., M.A.H., L.M.Z., C.J., M.A.P., T.L.B., K.A.B.), and the Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh (H.E.R., M.K.-L.) — both in Pittsburgh. Address reprint re

Acute Otitis media-1
Methods-1

- Inclusion
  - Age 6-23 months.
  - ≥2 doses of PCV-7 vaccine.
  - AOM
    - Onset ≤ 48 hours.
    - ≥ 3 on Acute Otitis Media Severity of Symptoms (AOM-SOS) scale by parents.
    - Middle-ear effusion + moderate or marked bulging of the TM or slight bulging of TM + otalgia or marked erythema of TM.

Acute Otitis media-2
Methods-2

- Randomization
  - 10 days of amoxicillin-clavulanate @ 90 mg/kg/d or placebo divided bid.
  - Parents and treating staff blinded.
- Assessments: day 1, 4-5, 10-12, 21-25.
- "Failure"
  - Day 4-5: lack of substantial improvement in symptoms or worsening on otoscopic exam
  - Day 10-12: incomplete resolution of symptoms and otoscopic signs (MEE OK)

Acute Otitis media-3
Results-1

- 291 randomized (144 antibiotics and 147 placebo)
- Global analysis: antibiotic group vs placebo group less likely to have evidence of clinical failure at or before day 4-5: 4% vs 23% ($p<0.001$), and at or before day 10-12: 16% vs 51% ($p<0.001$).
- NNT = 4.

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Acute Otitis media-4
Results-2

- Stratification analysis: clinical failure at or before day 10-12 same in both groups except:
  - AOM-SOS > 8: odds ratio = 2.2.
  - Bilateral AOM: odds ratio = 2.0.
  - Marked bulging of TM: odds ratio = 2.3.
- High risk features were cumulative.
- No difference in relapse rate.
- MEE rate 50% in antibiotic group and 63% in placebo group (P = 0.05).

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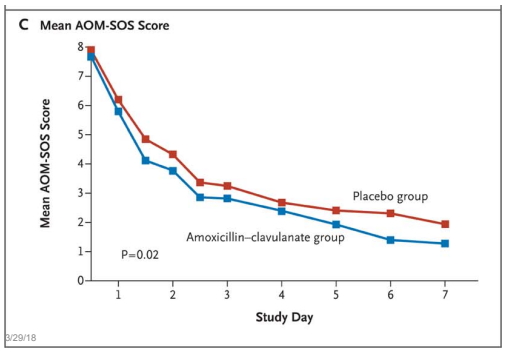
Acute Otitis media-5



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Pittsburgh AOM Data
Conclusions (My)

- In general, AOM is a self-resolving disease.
- Most "failures" are otoscopic, not symptomatic.
- The worse the disease (degree of illness, bilaterality, TM morphology), the greater the benefit of antibiotic therapy.
- 10 days of antibiotic therapy should be reserved for children with the very worst disease.

3/29/18

An evidenced based approach to reducing antibiotic use in children with acute otitis media: controlled before and after study

- Cates C.
- *BMJ 1999;318:715-716.*
- Manor View Practice, Bushey Health Centre, Bushey Hertfordshire, UK.

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Deferred antibiotics in AOM-2
Methods

- Change of office protocol
- AOM + "ill" child: antibiotics.
- AOM + "not particularly ill":
  - Handout on limited benefit of antibiotics in AOM
  - Antibiotic prescription for parents to fill if child did not get better "over a day or two."

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Deferred antibiotics in AOM-3
Results

- Median monthly prescriptions for amoxicillin fell from 75 to 47.
- Prescriptions for all antibiotics fell by 19%.
- Δ AOM/Total antibiotics: 50% to 33%.

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Deferred antibiotics in AOM-4
Conclusions

- Not all acute otitis media requires antibiotics.
- Parents' tolerance for "masterful inactivity" is more than is usually admitted.
- Educational efforts and risk sharing work well in an office based practice.
- Reduction in antibiotic use is feasible without denial of care.

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Deferred antibiotics in AOM
BMJ 2001;322:336-342

- Randomized controlled trial of immediate and delayed antibiotics in 315 children
- 93 general practices, SW England
- Age 6 mos - 10 years
- TM: dull or cloudy with redness, bulging, or perforation

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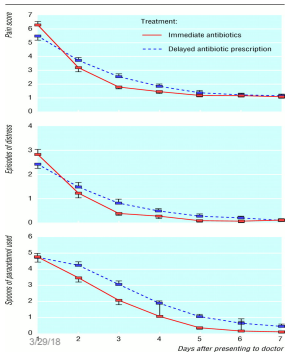
Deferred antibiotics-results



- 24% deferred group took antibiotics (usually by day 2)
- Effect of ABX group was ~ 1 days benefit
- No Δ days school missed
- 77% deferred parents satisfied

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Deferred antibiotics in AOM
Pediatrics 2005;115:1455-1465

- 223 children 6 m-12 y with "non-severe" AOM randomized to immediate antibiotics or "watchful waiting" (WW).
- "Severity" based on elaborate system
- Diagnosis of AOM standardized and supplemented by tympanography.
- "Failure" in WW: Rx = amoxicillin.
- Compliance measured (bottle weights).
- Outcome: symptom resolution (35 point scale) and recurrence rates (+others).

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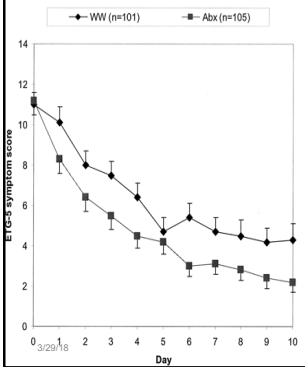
Deferred antibiotics in AOM-2



- 34% WW given antibiotics
- Failure rate age independent
- ABX group had ↑side-effects and ↑ residual Pen-R pneumococcus
- 30 day otoscopic outcome identical
- Parent satisfaction identical

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Follow-up of children with AOM not given antibiotics

JAMA Pediatrics 2016;170:1107

- 158 children, age 6-35 months, treated with deferred antibiotics. Reexamined in 48-72 hours.
- Of 104 children whose parents thought that they had "improved," 2.9% developed worse TM findings or perforation on otoscopy.
- Of 54 children with "symptomatic failure," 29.6% developed worse TM findings or perforation.

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Sample explanation

- Little Umbo has an ear infection. It doesn't look too bad. You know, most of these ear infections get better on their own in 2-3 days. If you are willing, I would like to defer antibiotics for now. But, I'm going to give you a prescription for amoxicillin to take with you. If in 2-3 days, your child isn't better, then start the antibiotics and give me a call. I'm sure this will work fine, because *you know your child best.*

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- Welcome to the era of "personalized medical care" = individualizing evaluation and management using clinical findings, selected ancillary testing, and sharing of uncertainty with families.

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Acute Otitis Media
The bottom line (My)

- There are two kinds AOM: purulent AOM and routine AOM.
- Purulent AOM [UK = "ill"]
  - = Very bulging TM, bilateral disease, draining ear, "sick" child.
  - Full course antibiotics usual but deferred antibiotics reasonable.
- Routine AOM [UK: "not particularly ill]
  - = Red, opaque, and/or mild-moderate bulging TM in "not particularly ill" child.
  - Deferred antibiotics usual but short-course antibiotics reasonable.

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