COMBINED EMERGENCY MEDICINE &
PEDIATRICS RESIDENCY
THE UNIVERSITY OF ARIZONA
Adults are just big kids

Neonatal Fever:
Past, Present & Future

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University of Arizona College of Medicine
Banner University Medical Center - Tucson

Disclosures

- I have no financial relationships or conflicts to disclose.

Objectives

- **How did we get here?**
  Review the changing epidemiology and evaluation strategies of neonatal fever
- **Where are we now?**
  Describe the changes in the AAP 2021 Neonatal Fever Guidelines
- **Where are we going?**
  Discuss new methods to improve the accuracy of neonatal fever evaluation on the horizon

Rule Out Sepsis

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Rule Out Sepsis

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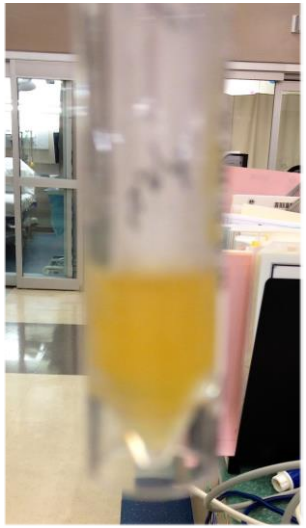
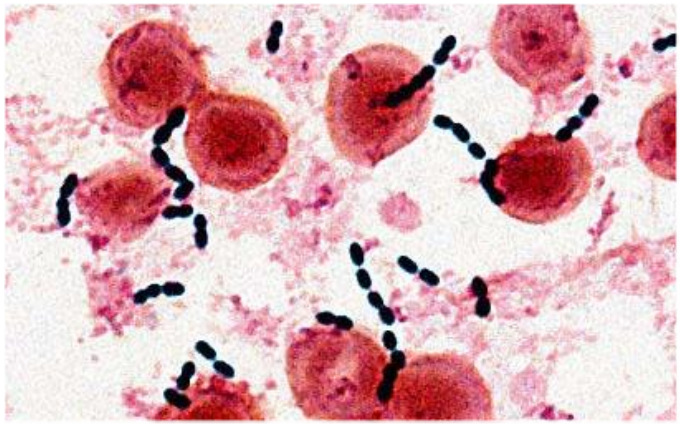
Invasive
Bacterial
Illness



Serious
Bacterial
Illness



Neonatal Fever Goals

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- **IDENTIFY** serious bacterial illness
- **EXCLUDE** serious bacterial illness
- **MINIMIZE** painful work up
- **AVOID** unnecessary antibiotics and hospitalization

in the

WELL-APPEARING FEBRILE INFANT

The “Well” Caveat

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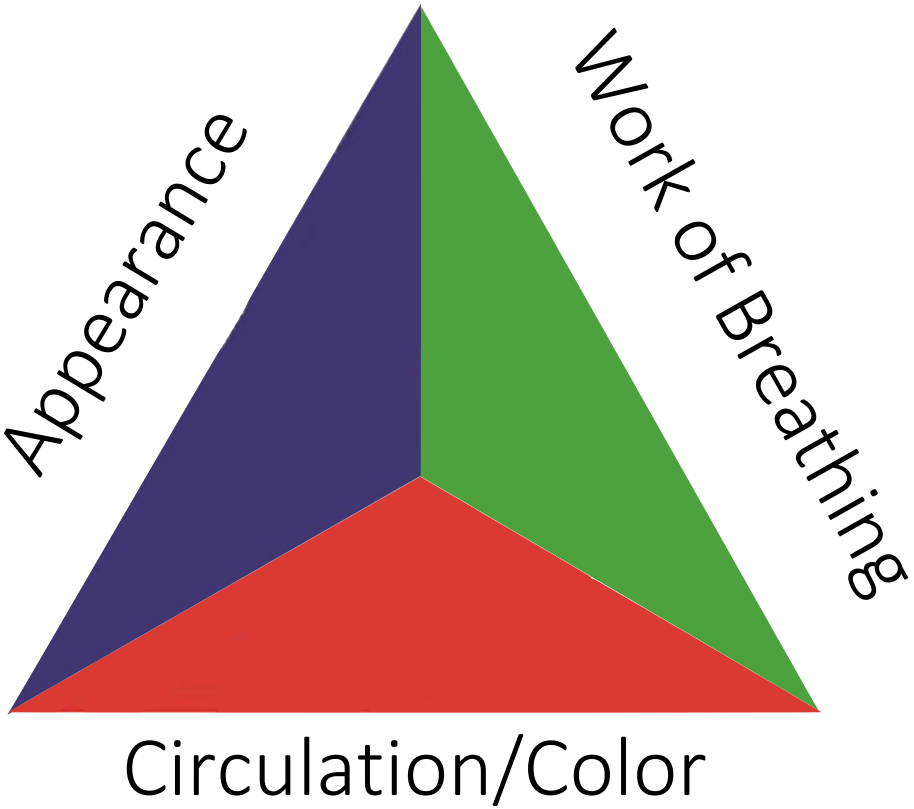

Dieckmann, R. A., Brownstein, D., & Gausche-Hill, M. (2010). The pediatric assessment triangle: a novel approach for the rapid evaluation of children. Pediatric emergency care, 26(4), 312-315.

The “Fever” Caveat

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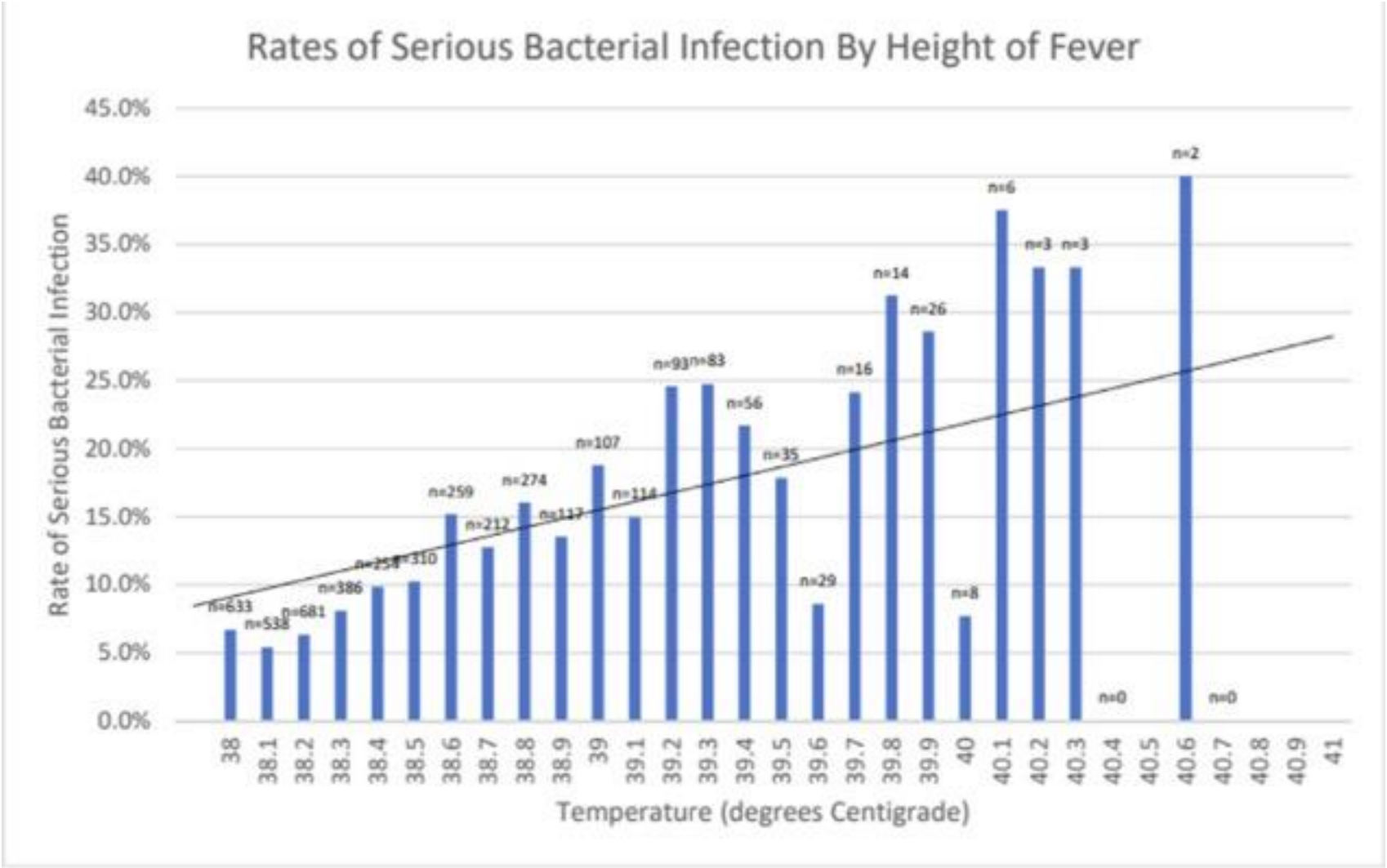

Davis, Joshua, and Erik Lehman. "Fever characteristics and risk of serious bacterial infection in febrile infants." The Journal of emergency medicine 57.3 (2019): 306-313.

The "Route" Caveat

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Fever in ED or Office

12.8% SBI Prevalence

Fever at Home

8.8% SBI Prevalence

Ramgopal, Sriram, et al. "Risk of serious bacterial infection in infants aged≤ 60 days presenting to emergency departments with a history of fever only." *The Journal of pediatrics* 204 (2019): 191-195.

The "Tactile Fever" Caveat

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- 91% of febrile infants were correctly identified by parents by feel
- 21% of afebrile infants were thought to have fever too
- Not a great indicator of SBI by itself

Does not necessitate entrance into the risk stratification pathways by itself

Callanan, Deborah. "Detecting fever in young infants: reliability of perceived, pacifier, and temporal artery temperatures in infants younger than 3 months of age." *Pediatric emergency care* 19.4 (2003): 240-243.

The "Bundling" Caveat

- 20 infants had continuous rectal temperatures for 2.5 hours
  - 12 given 1 blanket, 8 given 5 blankets and a hat
  - Mean temp change for "bundling" was +0.56°C
  - 2 infants reached 38.0°C
- It's *possible* for bundling to cause a fever
- Unbundling and rechecking RECTAL temp 15-30 min later is acceptable in an infant who has not received antipyretics

If uncertain, treat as a real fever

Cheng, Tina L., and J. Colin Partridge. "Effect of bundling and high environmental temperature on neonatal body temperature." Pediatrics 92.2 (1993): 238-240.

The “Infant” Caveat

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- <90 days
  - Historically has highest rate of SBI in children
- <60 days
  - Vaccination time
- <28 days
  - Official ”neonate” status
- <21 days
  - Higher risk of meningitis
- <14 days
  - Highest risk of invasive bacterial illness

Martinez, Elena, et al. "Prevalence and predictors of bacterial meningitis in young infants with fever without a source." The Pediatric infectious disease journal 34.5 (2015): 494-498.
Garcia, Silvia, et al. "Is 15 days an appropriate cut-off age for considering serious bacterial infection in the management of febrile infants?." The Pediatric infectious disease journal 31.5 (2012): 455-458.

The "SVI" Caveat

- ~80% of mothers did not know they had HSV
- Risk of HSV transmission:
  - Recurrent: 2%
  - Primary: 57%
- Increased Risk
  - HSV risk score ≥3

TABLE 3 Invasive HSV Risk Score

Factor	Point(s)
Age	
<14 d	3
14–28 d	2
>28 d	0
Seizure at home	2
Ill appearance[a]	2
Abnormal triage temperature[b]	1
Vesicular rash	4
Thrombocytopenia[c]	2
CSF pleocytosis[d]	2
Prematurity[f]	1

[a] "Sick, toxic, shocky," altered or decreased mental status, fussy, inconsolable, meningismus (ie, positive Kernig or Brudzinski sign or stiff neck), petechial rash, decreased perfusion, decreased pulses.[11]

[b] Triage temperature ≥38.0°C or <36.4°C.

[c] Platelets <150 000 per mm^3.

[d] CSF WBC count >15 cells per mm^3 if ≤28 d; ≥10 cells per mm^3 if >28 d.

[f] Birth before 37 wk gestation.

Cruz, Andrea T., et al. "Predictors of invasive herpes simplex virus infection in young infants." Pediatrics 148.3 (2021).

History of Neonatal Fever

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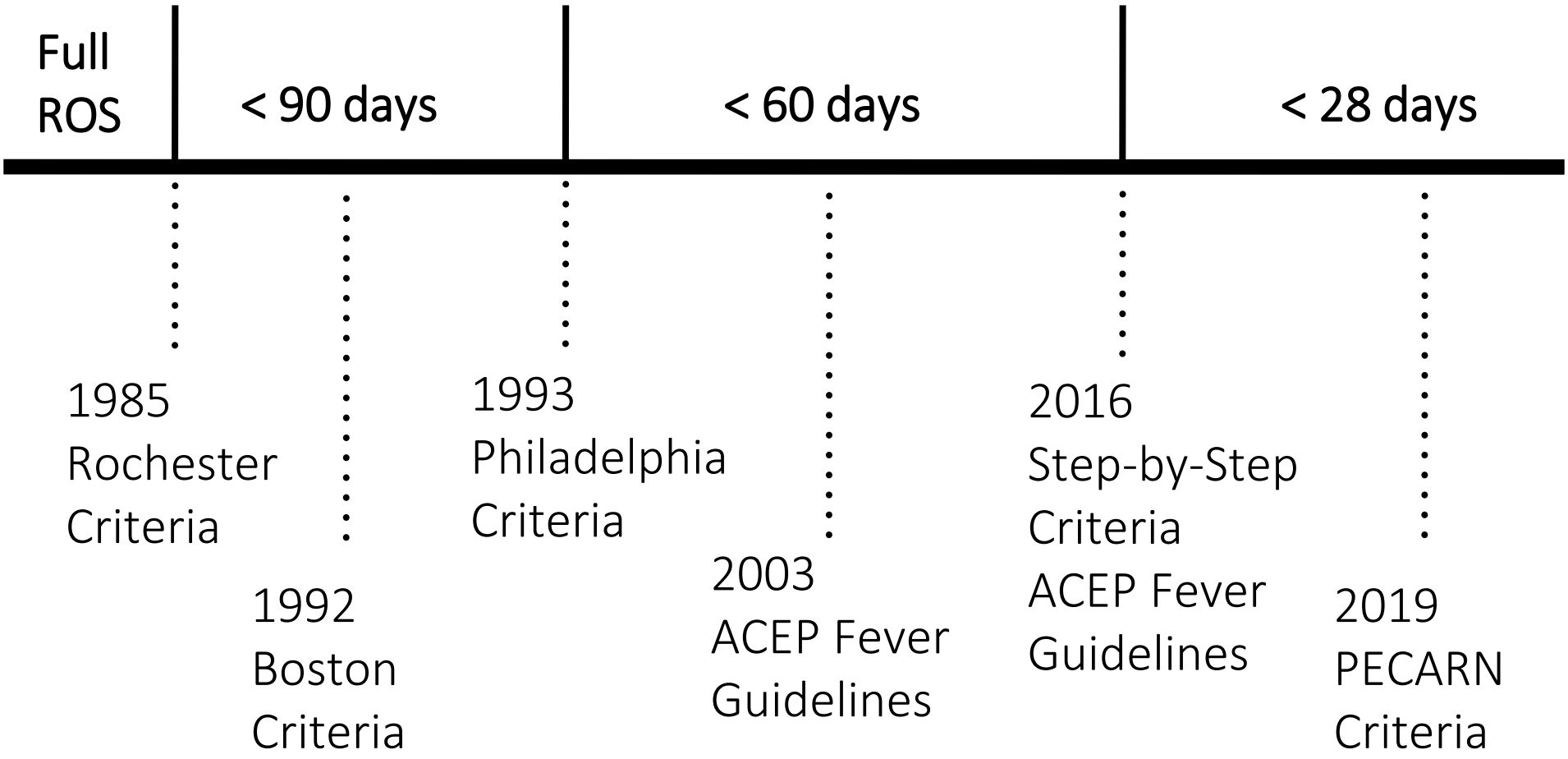
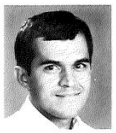


1980s

University Medical Center
Pediatric Housestaff • 1987–1988

Symbols:
MS-Medical School
PL-1 First Year Residency
PL-2 Second Year Residency
PL-3 Third Year Residency
PL-4 Fourth Year Residency

Adams, Cecilia
1st Year Resident
Ms — University of Colorado



Bezerra, Jorge
2nd Year Resident
MS — Federal University of Rio Grande do Norte
PL-1 University of Arizona

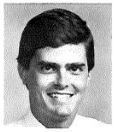
Blesch, Lauri
1st Year Resident
MS — University of Texas

Leslie Boyer Hassen
3rd Year Resident
MS-Harvard
PL-1, 2 Children's Hospital, Boston

Dalby, Susan L.
2nd Year Resident
MS — University of Arizona
PL-1 University of Arizona

D'Angelo, Sally
1st Year Resident
MS — University of Colorado

De Pasquale, John
1st Year Resident
MS — Temple University



Epps, Thomas E., Jr.
2nd Year Resident
MS — Med. Univ. So. Carolina
PL-1 University of Arizona

George, Kelly William
3rd Year Resident
MS — University of Nevada
PL-1, 2 University of Arizona

Gloudemans, Mary E.
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MS — University of Wisconsin
PL-1, 2 University of Arizona

Hall, Shanna D.
2nd Year Resident
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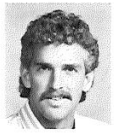
PL-1 University of Arizona

Hayes, Susan L.
2nd Year Resident
MS — University of Michigan
PL-1 University of Arizona

Hud, Joseph A., Jr.
2nd Year Resident
MS — Creighton
PL-1 University of Arizona

Lasala, Victoria E.
2nd Year Resident
MS — Michigan State University
PL-1 University of Arizona

Longoria, Teresa
2nd Year Resident
MS — Harvard
PL-1 University of Arizona

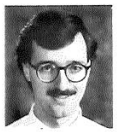


Luhn, Roger D.
2nd Year Resident
MS — UCSD
PL-1 University of Arizona

McDonald, Fred, W.
3rd Year Resident
MS — NY Coll. Osteopathic Med.
PL-1 Geisinger Med. Center
PL-2 University of Arizona

Meehan, David J.
2nd Year Resident
MS — Univ. Missouri-Columbia
PL-1 University of Arizona

Ostrowski, Carole A.
3rd Year Resident
MS — Loyola-Stritch
PL-1, 2 University of Arizona



Ratl, Habib
3rd Year Resident
MS — American University of Beirut
PL-1 American University of Beirut
PL-2 University of Arizona

Rehan, Ann
1st Year Resident
MS — University of Iowa

Rojas, Oscar I.
2nd Year Resident
MS — Med. Coll. of Wisconsin
PL-1 University of Arizona

Samson, Ricardo
1st Year Resident
MS — University of Michigan

Savitt, Gregg J.
3rd Year Resident
MS — University of Minnesota
PL-1, 2 University of Arizona

Seaver, Laurie
1st Year Resident
MS — University of Arizona

Robert Serlin
1st Year Resident
Albert Einstein
PL-1 University of Wisconsin
PL-2 St. Vincent's Hospital, Mass.
PL-3, 4 University of Alberta

Smith, Susan
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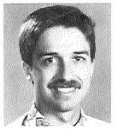
MS — University of Colorado

Stevenson, Mark M.
2nd Year Resident
MS — Oregon Health Sciences Univ.
PL-1 University of Arizona

Stilson, Michael
3rd Year Resident
MS — University of Colorado
PL-1, 2 University of Arizona

Swinyard, Michael
4th Year Resident
MS — University of Utah
PL-1, 2, 3 University of Arizona



Tarantino, Michael
1st Year Resident
MS — University of Wisconsin

Yancey, Asa G., Jr.
3rd Year Resident
MS — Boston University
PL-1 Phoenix Hospitals Affiliated Peds Prog
PL-2 University of Arizona

Zimmerman, Mary B.
3rd Year Resident
MS — University of Arizona
PL-1, 2 University of Arizona

Rochester Criteria

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Adults are just big kids

- 233 well appearing infants < 90 days
- No skeletal, soft tissue, skin or ear infections
- Full term, no prior illness, hospitalizations
- No prior antibiotics
- No Hyperbilirubinemia
- No chronic or underlying illness

LOW RISK CRITERIA

- White Blood Cell count normal (5000 to 15,000/mm3)
- Band Neutrophils < 1,500/mm3
- Urine White Blood Cells <10 per hpf

Conclusion:

Not all febrile infants have SBI.
Not all febrile infants need to be hospitalized.
But we're not sure who is safe to go home.

Dagan, Ron, et al. "Identification of infants unlikely to have serious bacterial infection although hospitalized for suspected sepsis." *The Journal of pediatrics* 107.6 (1985): 855-860.

Rule Out Sepsis

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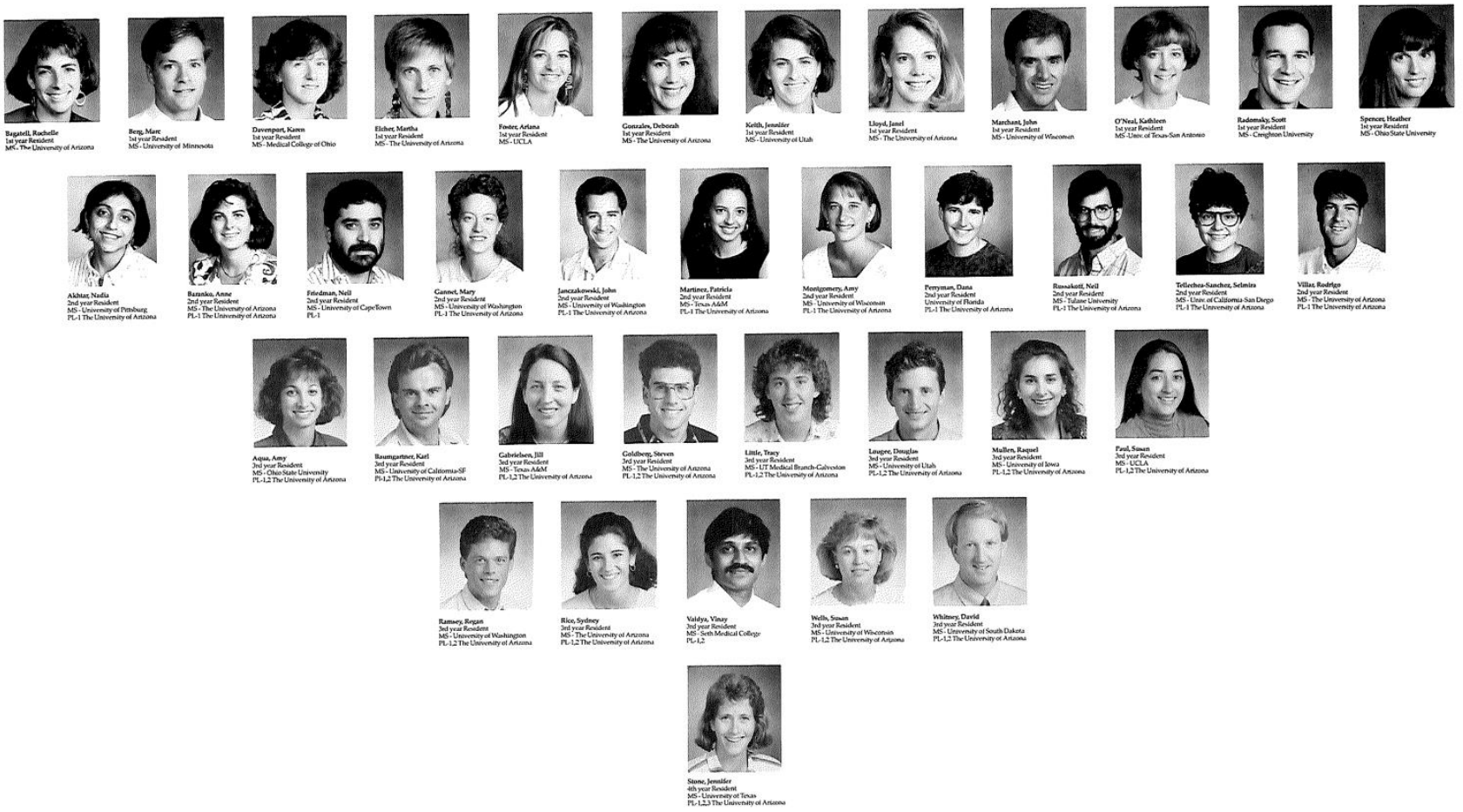
Adults are just big kids

<90 days

1990s

Pediatric Housestaff 1993-94

MS: Medical School
PL-1: First Year Residency
PL-2: Second Year Residency
PL-3: Third Year Residency
PL-4: Fourth Year Residency



Boston Criteria

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Adults are just big kids

- 503 well appearing infants 28 - 89 days
- No skeletal, soft tissue, skin or ear infections
- Full term, no prior illness, hospitalizations
- No prior antibiotics
- No Hyperbilirubinemia
- No chronic or underlying illness

LOW RISK CRITERIA

- White Blood Cell count normal (<20,000/mm3)
- Band:Neutrophils < 0.2
- If Diarrhea is present, Fecal Leukocytes <5 per hpf
- Urine White Blood Cells <10 per hpf
- CSF <10 WBC/mm3
- Normal CXR

Conclusion:

Low risk patients can be discharged home provided they have blood, urine and CSF cultures and get Ceftriaxone just in case

Baskin, Marc N., Edward J. O'Rourke, and Gary R. Fleisher. "Outpatient treatment of febrile infants 28 to 89 days of age with intramuscular administration of ceftriaxone." The Journal of pediatrics 120.1 (1992): 22-27.

Boston Cutoffs

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Adults are just big kids

28-89 days





<28 days





Boston Cutoffs

Combined Emergency Medicine & Pediatrics Residency
The University of Arizona
Adults are just big kids

28-89 days




<28 days





Philadelphia Criteria

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Adults are just big kids

- 747 well appearing infants 28 - 56 days
- No skeletal, soft tissue, skin or ear infections
- Full term, no prior illness, hospitalizations
- No prior antibiotics
- No Hyperbilirubinemia
- No chronic or underlying illness

LOW RISK CRITERIA

- White Blood Cell count normal (5000 to 15,000/mm3)
- Band:Neutrophils < 0.2
- If Diarrhea is present, Fecal Leukocytes <5 per hpf
- Urine White Blood Cells <10 per hpf
- CSF <8 WBC/mm3
- Normal CXR

Conclusion:

Low risk patients can be discharged home without antibiotics provided they have blood, urine and CSF cultures

Baker, M. Douglas, Louis M. Bell, and Jeffrey R. Avner. "Outpatient management without antibiotics of fever in selected infants." *New England Journal of Medicine* 329.20 (1993): 1437-1441.

Philadelphia Cutoffs

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Adults are just big kids

29-89 days




<28 days





Philadelphia Cutoffs

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Adults are just big kids

29-56 days



<28 days





2000s

Pediatric Housestaff 2005-2006

THE UNIVERSITY OF ARIZONA HEALTH SCIENCES CENTER

PL - 1's


Cavallaro, Elizabeth


Fung, Rebecca


Gruchala, Nancy


Hainstock, Michael


Kisling, Kara


Kothari, Samip


Mansfield, Erin


Munkwitz, Michele


Ochoa-Buck, Julissa


Sathre, Lisa


Tortorice, Lisa


Young, Ryan

PL - 2's


Bierer, Ryann


de la Torre, Alejandro


Foster, Christopher


Hahn, Melissa


McLain, Erin


Montes, Clarisa


Murray, Christopher


Schimelpfenig, Sam


Thompson, Kelly


Van Handel, Jeminah


Wicks, Chelsea


Witt, Scott

PL - 3's


Delp, Zebulon


Estrada, Franchesca


Fimbres, Angela


Friedman, Brad


Grahn, Kirstin


Johnson, Ryan


Khurmi, Rupal


Lowe, Chan


Mulcahy, Jean


Seckeler, Michael


Shih, Sabrina


Timock, Joshua

Combined EM/Pediatrics


Bradshaw, Hans


Gillespie, Charles

Pediatric Chief Residents


Bier, Angela


Zarate, Angela

SBI Rate/Type Changes

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1980s		*2010s*
3 - 20%	**Overall Incidence**	**8 - 13%**
0 - 14%	Bacterial Meningitis	0.4-0.6%
20 - 30%	Bacteremia	1.8-2.4%
30 - 50%	UTI	92%

Greenhow, Tara L., et al. "The changing epidemiology of serious bacterial infections in young infants." The Pediatric infectious disease journal 33.6 (2014): 595-599.
McCulloh, Russell J., et al. "Prevalence of invasive bacterial infections in well-appearing, febrile infants." Hospital Pediatrics 11.9 (2021): e184-e188.

Co-Infection

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SBI	<28 days +Virus	>28 days +Virus	<28 days - Virus	>28 days - Virus
Any	4.2%	3.4%	16.9%	9.9%
Meningitis	0.8%	0.2%	1.7%	0.2%
Bacteremia	1.1%	0.6%	4.4%	1.8%
UTI	2.6%	2.8%	13.3%	8.8%

Mahajan, Prashant, et al. "Risk of bacterial coinfections in febrile infants 60 days old and younger with documented viral infections." *The Journal of pediatrics* 203 (2018): 86-91.

2010s

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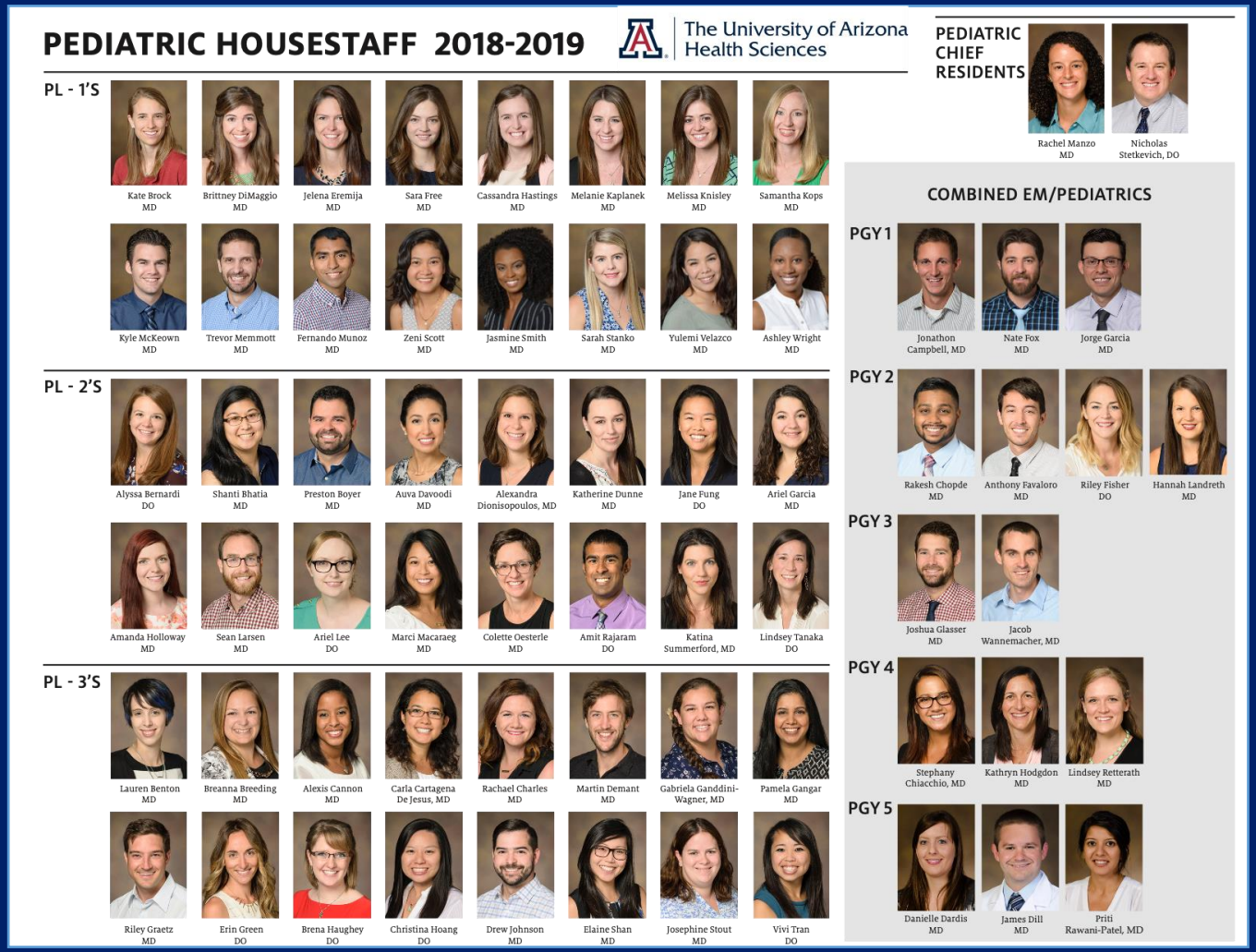

Step-by-Step Criteria

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- Multi-center retrospective trial
- 2185 well appearing infants <90 days
- No obvious source of fever
- Unclear if they included patients with complicated PMHx, prematurity, etc.

INTERMEDIATE RISK CRITERIA

- Well-appearing according to PAT
- Age > 21 days
- Urine White Blood Cells <10 per hpf
- Procalcitonin <0.5ng/mL

LOW RISK CRITERIA

- All of the above AND
  - CRP <20mg/L and ANC <10,000/mm^3

Conclusion:

Low risk patients can be discharged home without antibiotics OR lumbar puncture so long as fever is well established.

Mintegi, Santiago, et al. "Accuracy of a sequential approach to identify young febrile infants at low risk for invasive bacterial infection." Emergency Medicine Journal 31.e1 (2014): e19-e24.
Gomez, Borja, et al. "Validation of the "step-by-step" approach in the management of young febrile infants." *Pediatrics* 138.2 (2016): e20154381.

PECARN Criteria

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- Multi-center prospective derivation/validation trial
- 1821 well appearing infants <60 days
- No obvious infection
- Full term, no chronic medical problems
- No prior antibiotics

LOW RISK CRITERIA

- Negative UA:
  - Negative leukocyte esterase
  - Negative nitrites
  - White Blood Cells <5 per hpf
- ANC <4.09/mL
- Procalcitonin <1.71 ng/mL

Conclusion:

Low risk patients can be discharged home without antibiotics OR lumbar puncture if > 28 days.

Kuppermann, Nathan, et al. "A clinical prediction rule to identify febrile infants 60 days and younger at low risk for serious bacterial infections." *JAMA pediatrics* 173.4 (2019): 342-351.

New CDT Cutoffs

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Adults are just big kids

29-60 days



<28 days





New CDT Cutoffs

Combined Emergency Medicine & Pediatrics Residency
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Adults are just big kids

22-60 days

<21 days

2020s

Big Changes

CLINICAL PRACTICE GUIDELINE

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

Clinical Practice Guideline: Evaluation and Management of Well-Appearing Febrile Infants 8 to 60 Days Old

Robert H. Pantell, MD, FAAP,[a] Kenneth B. Roberts, MD, FAAP,[b] William G. Adams, MD, FAAP,[c] Benard P. Dreyer, MD, FAAP,[d] Nathan Kuppermann, MD, MPH, FAAP, FACEP,[e] Sean T. O'Leary, MD, MPH, FAAP,[f] Kymika Okechukwu, MPA,[g] Charles R. Woods Jr, MD, MS, FAAP[h] SUBCOMMITTEE ON FEBRILE INFANTS

Outside of Guidelines

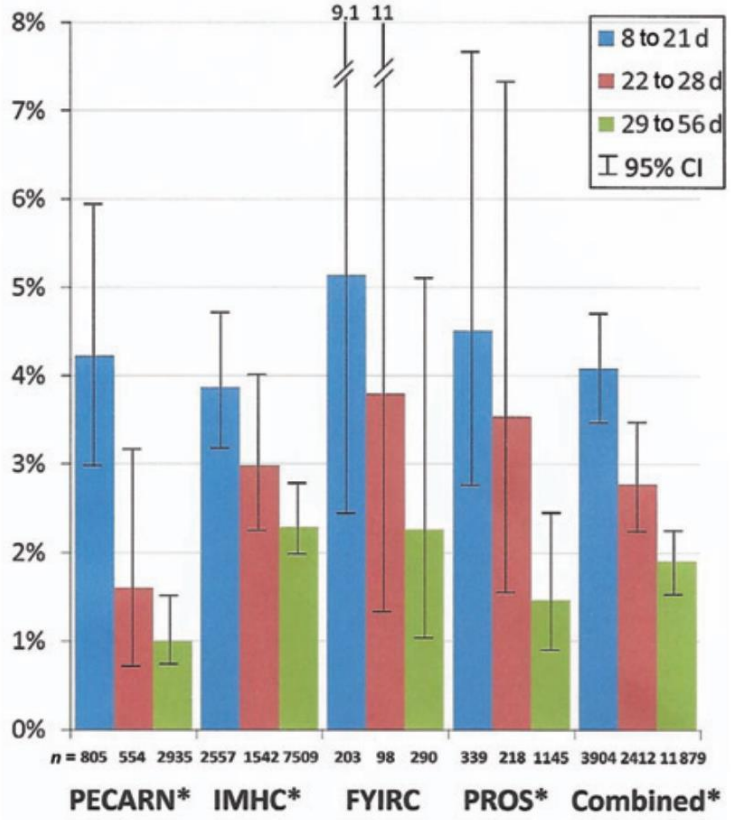
- < 37 weeks
- < 2 weeks + maternal fever/infxn/abx
- Visible HSV or focal bacterial infxn
- Clinical bronchiolitis **with or without a positive test**
- Documented immune compromise
- Tech-dependent, congenital anomalies, complicated neonatal course
- Immunization within 48 hours

Included in Guidelines

- Respiratory symptoms not c/w bronchiolitis
- Diarrhea
- Otitis media
- Current or recent antibiotics use (requires “individualized interpretation of febrile infant pathway”)
- Positive viral tests

Age Cutoffs

"Because risk of IBI has extensively been documented to steadily decline over the first few months, any day or week cutoff is arbitrary and subject to interpretation depending on a clinician's or a parent's risk aversion or tolerance."



New Age Cutoffs: 8-21d, 22-28d, 29-60d

End of Mandatory Culture?

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- Positive Urinalysis
  - Any leukocyte esterase, nitrites or pyuria
- Positive urine culture
  - >10K cfu WITH pyuria and fever
  - **NNT = 200-500 to catch 1 UTI with neg LE**

Positive urine culture with normal urinalysis likely to represent asymptomatic bacteriuria or contamination.

Bag Urine for Urinalysis?

- New recommendations allow for options in >22d:
  - Ideal is SPA or catheterization
  - May offer bag urine for urinalysis ONLY

Negative urinalysis is NOT a UTI

Positive urinalysis requires a SPA or cath specimen for culture

Inflammatory Markers

- Suggested markers
  - TMax >38.5ºC
  - ANC >4000 (PECARN) or >5200 (FYIRC)
  - PCT >0.5ng/mL
  - CRP >20mg/dL (used when PCT unavailable)

Best to use existing IMs according to existing clinical decision tools

No Lumbar Puncture?

- Most new CDTs reasonably exclude meningitis
  - For 22-28d, NNT 1000-1500 depending on IMs
  - For 29-60d, NNT 4000, 0.025% chance of missing meningitis
- Urinalysis not a factor in consideration of LP
  - No correlation with UTI and meningitis in this age group
  - False positive CSF pleocytosis with febrile UTI

Hospital observation without LP or antibiotics is safe and may be preferable

Observation at Home?

- For 22-28 days, can observe at home if:
  - Urinalysis is normal
  - No IM obtained is abnormal
  - CSF is obtained and is normal or enterovirus +
  - IV antibiotics given
  - Return precautions emphasized
  - 24 hours follow up secured
  - Safe discharge with access to care

May consider home observation with strict criteria +/- a dose of ceftriaxone

Observation at Home?

- For 29-60 days, can observe at home if:
  - No IM obtained is abnormal
  - Blood cultures sent
  - Return precautions emphasized
  - 24 hours follow up secured
  - Safe discharge with access to care

May consider home observation with strict criteria without LP or antibiotics

Oral Antibiotics for UTI?

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- For 29-60 days, can treat UTI outpatient if:
  - No IM obtained is abnormal
  - Blood cultures sent
  - Oral cephalexin or cefixime
  - Return precautions emphasized
  - 24 hours follow up secured
  - Safe discharge with access to care

May consider oral therapy for UTI with strict criteria without LP

Future

The University of Arizona Pediatric Residency Program Class of 2026

Yousef Abdulrahman

Lekarská Fakulta, Univerzity Karlovy

Sara Bertram

University of Nevada, Reno School of Medicine

Will Byrne-Quinn

Rocky Vista University College of Osteopathic Medicine

Ajuni Choudhary

Burrell College of Osteopathic Medicine at New Mexico State University

Trevor Dickey

The University of Texas Health Science Center at San Antonio Joe R. and Teresa Lozano Long SOM

Elizabeth Drda

Pennsylvania State University College of Medicine

Sierra Forbush

Western University of Health Sciences College of Osteopathic Medicine of the Pacific

Yousra Ghoweba

University of Sharjah College of Medicine

Kyle Goble

Medical College of Georgia at Augusta University

Kyle Kener

Texas Tech University Health Sciences Center Paul L. Foster School of Medicine

Camille LeBlanc

University of New England College of Osteopathic Medicine

Emilie No

Western University of Health Sciences College of Osteopathic Medicine of the Pacific

Ann O'Connell

University of North Dakota School of Medicine and Health Sciences

Francisco Romo

University of Arizona College of Medicine - Tucson

Rebecca Goulson
University of Minnesota

Ageline Salas
Weill Cornell Medicine

Diego Urbina
University of Arizona

Aronson Criteria

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- Retrospective case control derivation/validation study
- 181 infants with IBI and 362 case controls matched 1:2
- Low risk: Sens 99.5-99.8%/ Spec 22.7-31.3%
  - Missed 2 bacteremia in the derivation study
  - Missed 3 bacteremia and 1 meningitis in retrospective validation study

IBI Scoring System

• Age < 21 days	1 Point
• ED Tmax 38.0 - 38.4°C	2 Points
• ED Tmax ≥38.5°C	4 Points
• Abnormal UA	3 Points
• ANC ≥5185/µL	2 Points
Low Risk:	0-1 Point
Moderate Risk:	2-3 Points
High Risk:	4-10 Points

Potential: Fever at home only with everything else normal, may be monitored at home regardless of age . . . ?

Aronson, Paul L., et al. "A prediction model to identify febrile infants≤ 60 days at low risk of invasive bacterial infection." Pediatrics 144.1 (2019).
Tsai, Stacy J., and Sriram Ramgopal. "External Validation of an Invasive Bacterial Infection Score for Young Febrile Infants." Hospital Pediatrics 11.3 (2021):

Machine Learning Criteria

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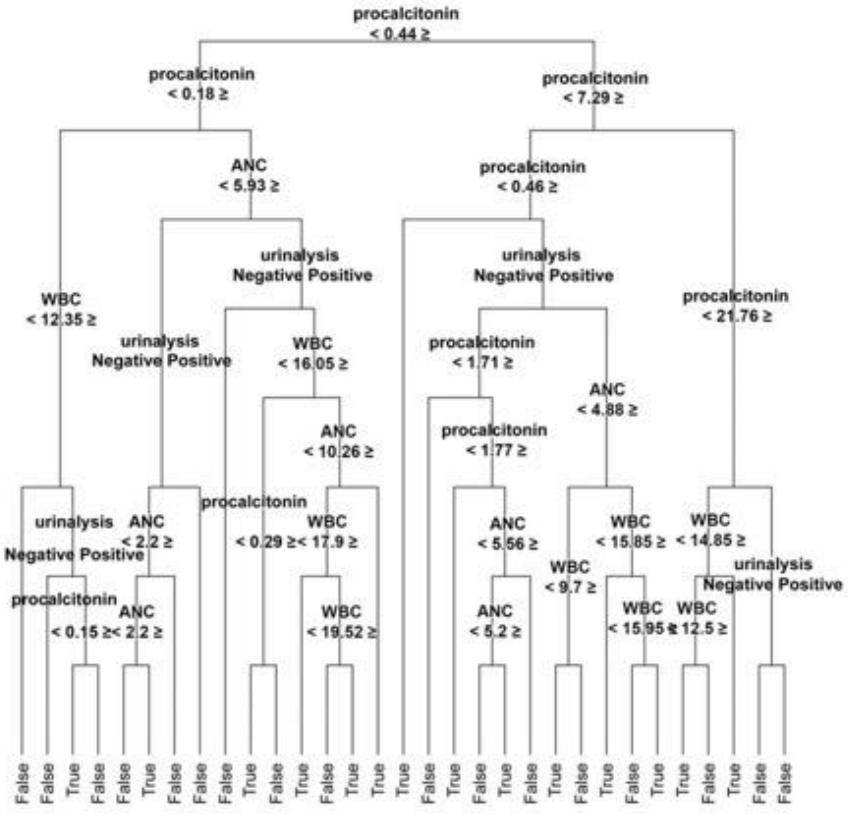
- Retrospective multicenter derivation/validation study utilizing 4 different machine learning models
- 1470 infants well appearing infants <60 days
- Low risk Sens 98.6-100%/ Spec 74.9-81.8%
  - Missed 1 bacteremia that also was missed by PECARN and Step-by-Step



Potential: Machine learning based on the patient in front of you to determine risk for SBI.

Ramgopal, Sriram, et al. "Machine learning to predict serious bacterial infections in young febrile infants." Pediatrics 146.3 (2020).

Biosignatures

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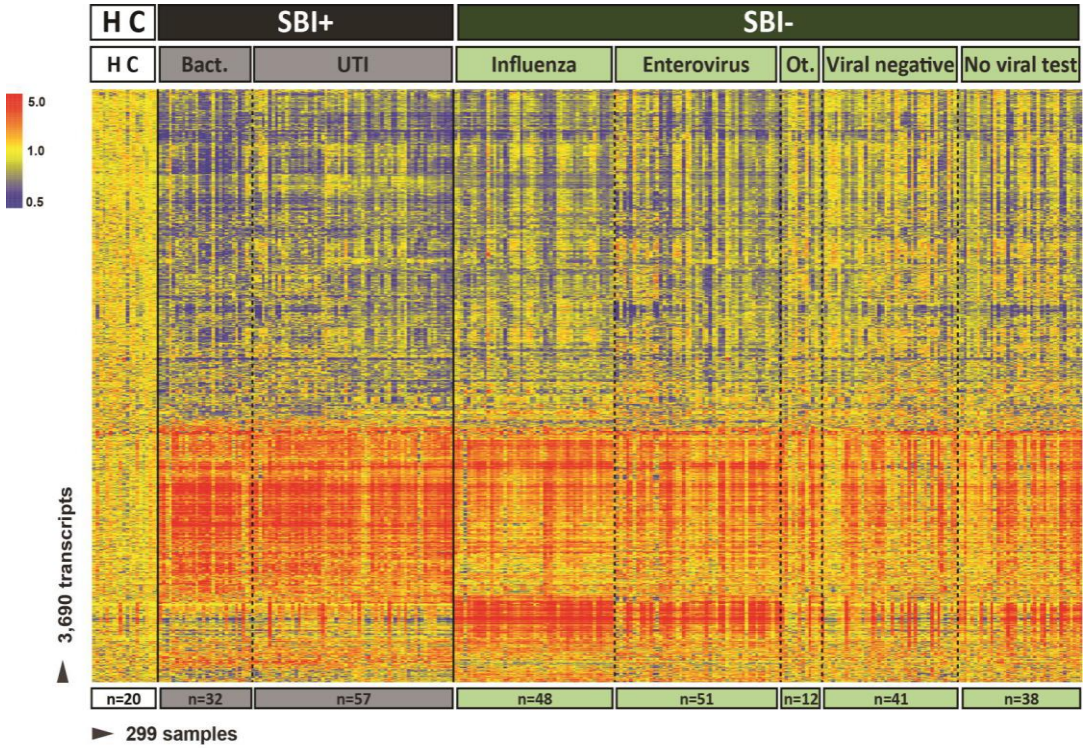

- Sensitivity 94%, Specificity 95%
- Post-test probability of Bacteremia 0.2%
- Post-test probability of Meningitis 0%

Mahajan, Prashant, et al. "Association of RNA biosignatures with bacterial infections in febrile infants aged 60 days or younger." Jama 316.8 (2016): 846-857.

Biosignatures

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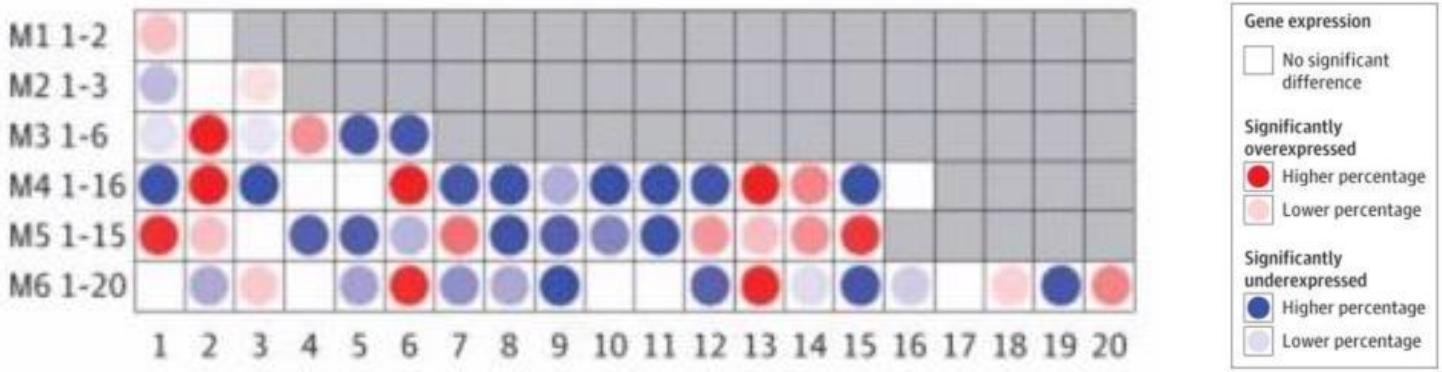

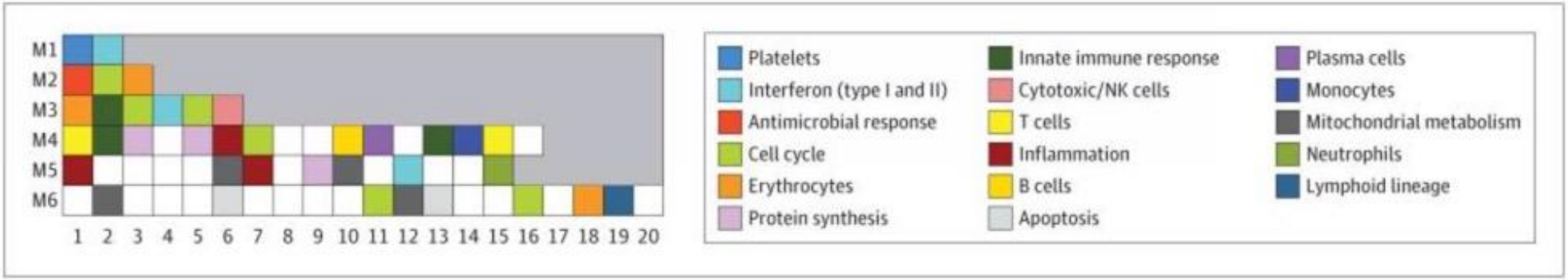

Potential:

Distinguish viral from bacterial

Distinguish pathogen from contaminant

Be run on a PCR platform with 2-4 hour turnaround

Outperform traditional cultures

Mahajan, Prashant, et al. "Association of RNA biosignatures with bacterial infections in febrile infants aged 60 days or younger." Jama 316.8 (2016): 846-857.

Summary

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28-89 days





<28 days





Summary

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~22-60 days

<21 days

History of Neonatal Fever

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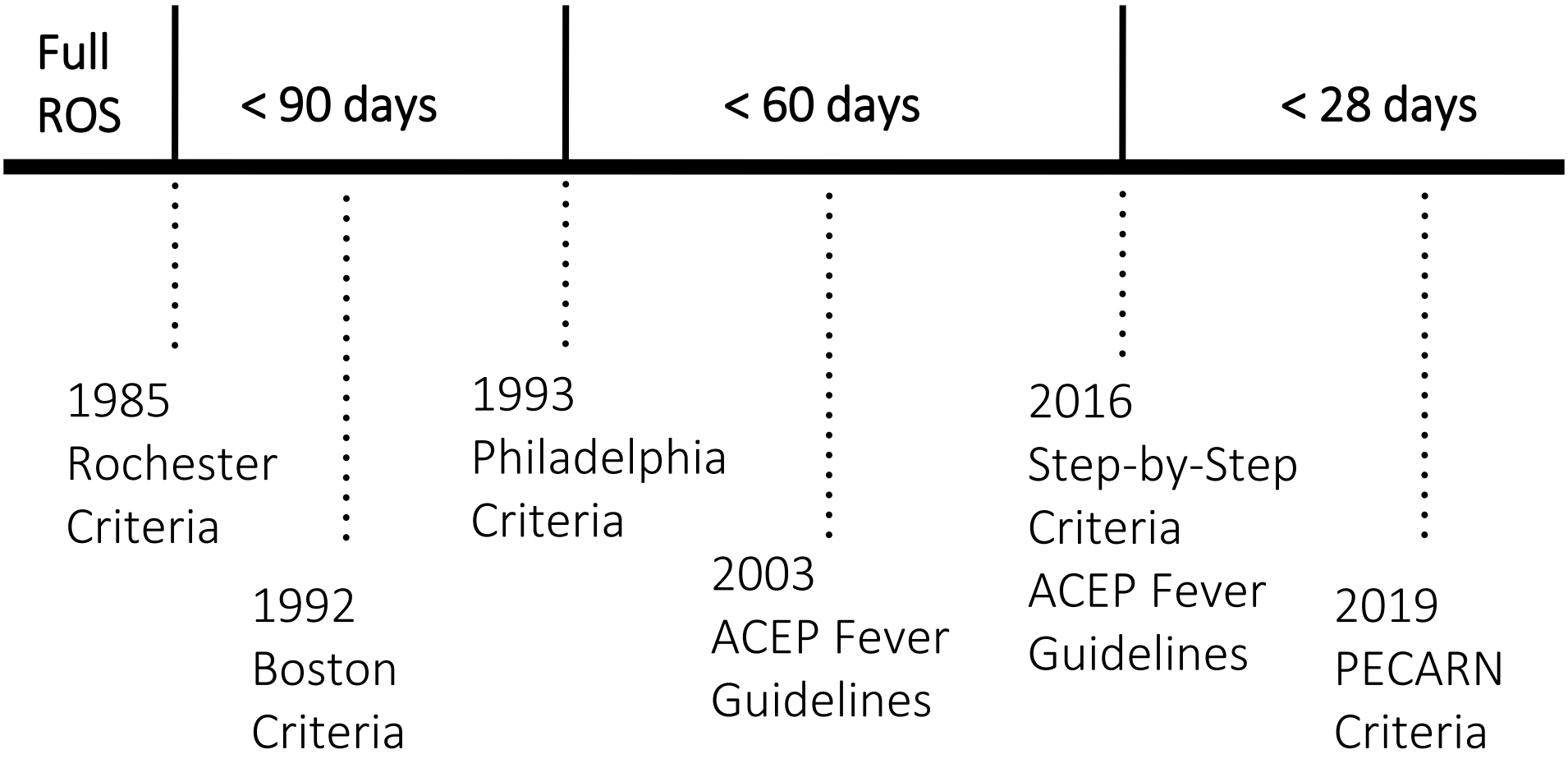

Summary

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Full ROS	< 90 days	< 60 days	< 28 days	No Mandatory ROS

Refined CDTs
Better tests

Thank you all

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