Pediatric Mysteries (including FWS / FUO)

13 June 2017

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Duke Pediatric Infectious Diseases

Disclosures

- Advisory board member for GSK (for belimumab pregnancy registry).
- Co-founder of Grid Therapeutics (formerly Cue Biologics).
- Chief Medical Officer, DHVI.

Learning Objectives

- Describe the differences between FUO and FWS.
- Recommend appropriate diagnostic tests for these conditions.
- Prescribe appropriate therapy.

What I will talk about

- Fever without source (FWS)
- Fever of unknown origin (FUO)
- Recurrent infections

Case 1

10 yo ♀ with recurrent fevers to 102˚ F daily for six weeks

- also has generalized malaise
- unusual rash on legs
- good workup by PMD
- family worried

Case 2

8 mo ♂ with third episode of pneumonia

- growth reasonable
- no FHx of recurrent illnesses
- CXR with multifocal infiltrates
- PMD worried

Case 3

5 yo ♀ with daily fevers increasing in height for four weeks

- some cervical lymphadenopathy
- tired look
- initial lab work normal
- weight curve has flattened

Commonalities

in each case

- symptoms not explained by typical childhood illness patterns
- persistence beyond the norm
- “ain’t right”

Definitions

fever without source (FWS)

fever of recent onset

no adequate explanation based on history and physical exam

Definitions

fever without source (FWS)

≡ fever without localizing signs

Definitions

fever of unknown origin (FUO)

fever of >7 days duration

no diagnosis after initial work-up

The Distinction

FWS vs. FUO

differential diagnoses different

needs more immediate evaluation

can take a more thoughtful approach

FWS

fever without source (FWS)

fever of recent onset
(<1 week)

FWS

fever without source (FWS)

no adequate explanation based on history and physical exam

(should be careful H+P)

FWS—Epidemiology

5-10% (22%) of children with fever lack localizing signs

peak incidence in 2nd year of life

estimated a practicing pediatrician sees this once every 4-5 days

FWS

some are presenting with a new chronic illness

some are gravely ill

most are not

FWS

the evaluation is a bit like panning for gold…

you must always pay attention!

FUO

FUOs are different

you are out of the acute stage

you have already done a work-up

FUO

two approaches to further work-up

test for everything at once

test in a stepwise fashion

FUO—Epidemiology

most have uncommon presentations of common illnesses

case series—
only 5 of 418 had rare disorder

FUO—Epidemiology

most series state that 10-20% of cases never get a diagnosis (50%)

unlike adults, most children get better

FUO

in cases of FUO, three services are routinely consulted

Infectious Diseases

Rheumatology

Hematology/Oncology

Infectious Diseases

Hematology/
Oncology

Rheumatology

FUO—Epidemiology

most case series report that diagnoses are

infectious >

rheumatologic >

oncologic

FWS & FUO

direct your work-up with two principles in mind

1. Look for things that are common.
2. Look for things that will kill you.

FWS—Rational Work-up

historically, two worrisome illnesses

meningitis

bacteremia

and a third (UTI) that could be hard to diagnose

Bacterial disease in FWS

neonates (0-3 months)

Streptococcus agalactiae

Escherichia coli

Listeria monocytogenes

Bacterial disease in FWS

infant / toddler (3 mos to 3 yrs)

Haemophilus influenzae type B

Streptococcus pneumoniae

Neisseria meningitidus

Bacterial disease in FWS

children / adolescents (3-19+ yrs)

Streptococcus pneumoniae

Neisseria meningitidus

Historical FWS

historically, 3-5% of children with FWS had bacteremia

and, 5-10% of those would develop meningitis if not treated

Historical FWS

historically, 3-5% of children with FWS had bacteremia

plus, 10% would develop a localized infection

Historical FWS

historically, 3-5% of children with FWS had bacteremia

and, 30% would have persistence of bacteremia

Historical FWS

historically, 3-5% of children with FWS had bacteremia

overall badness rate of

1.4-2.5%

Shifting FWS

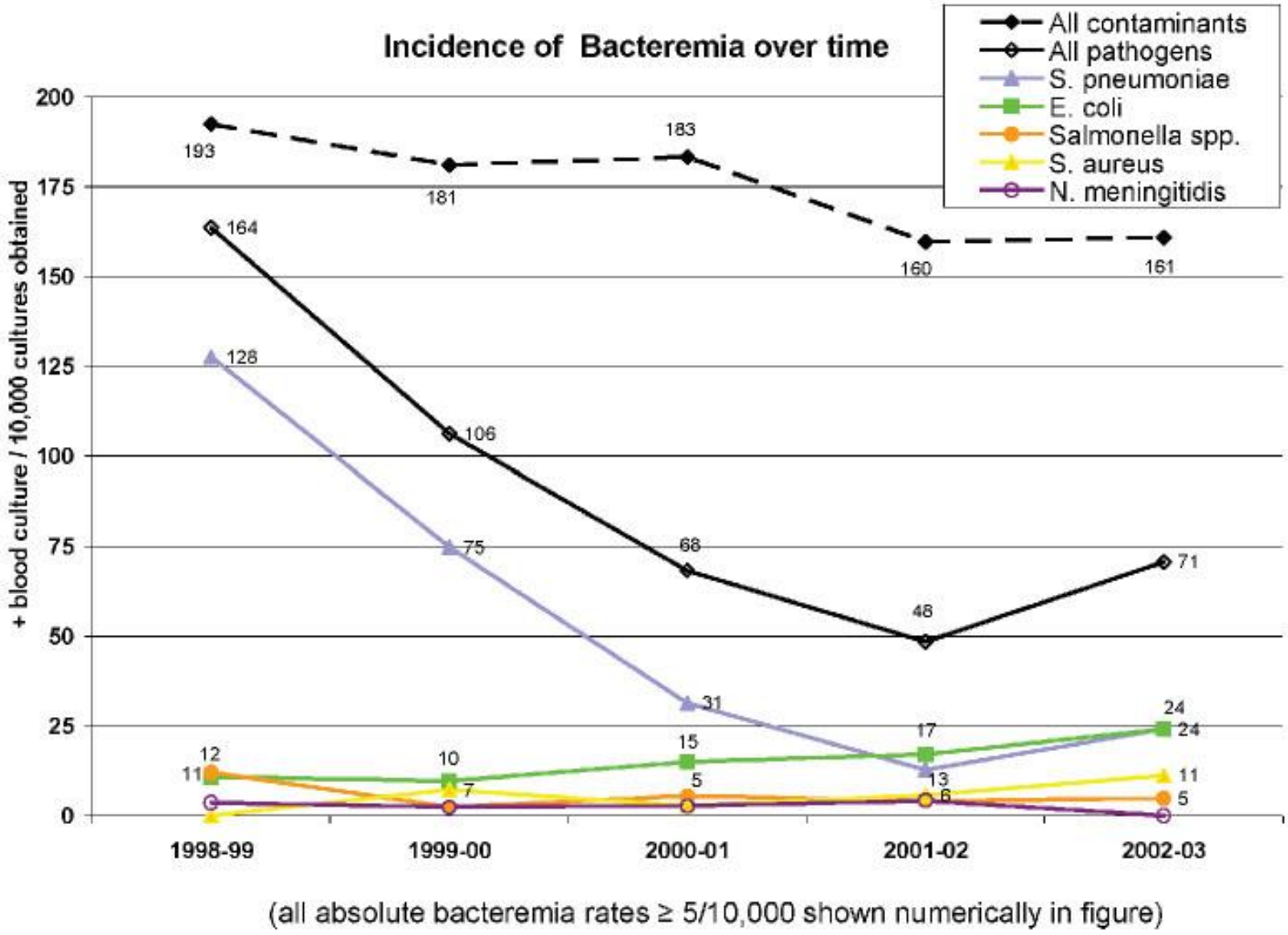
we now have excellent vaccine coverage against

Haemophilus influenzae type B

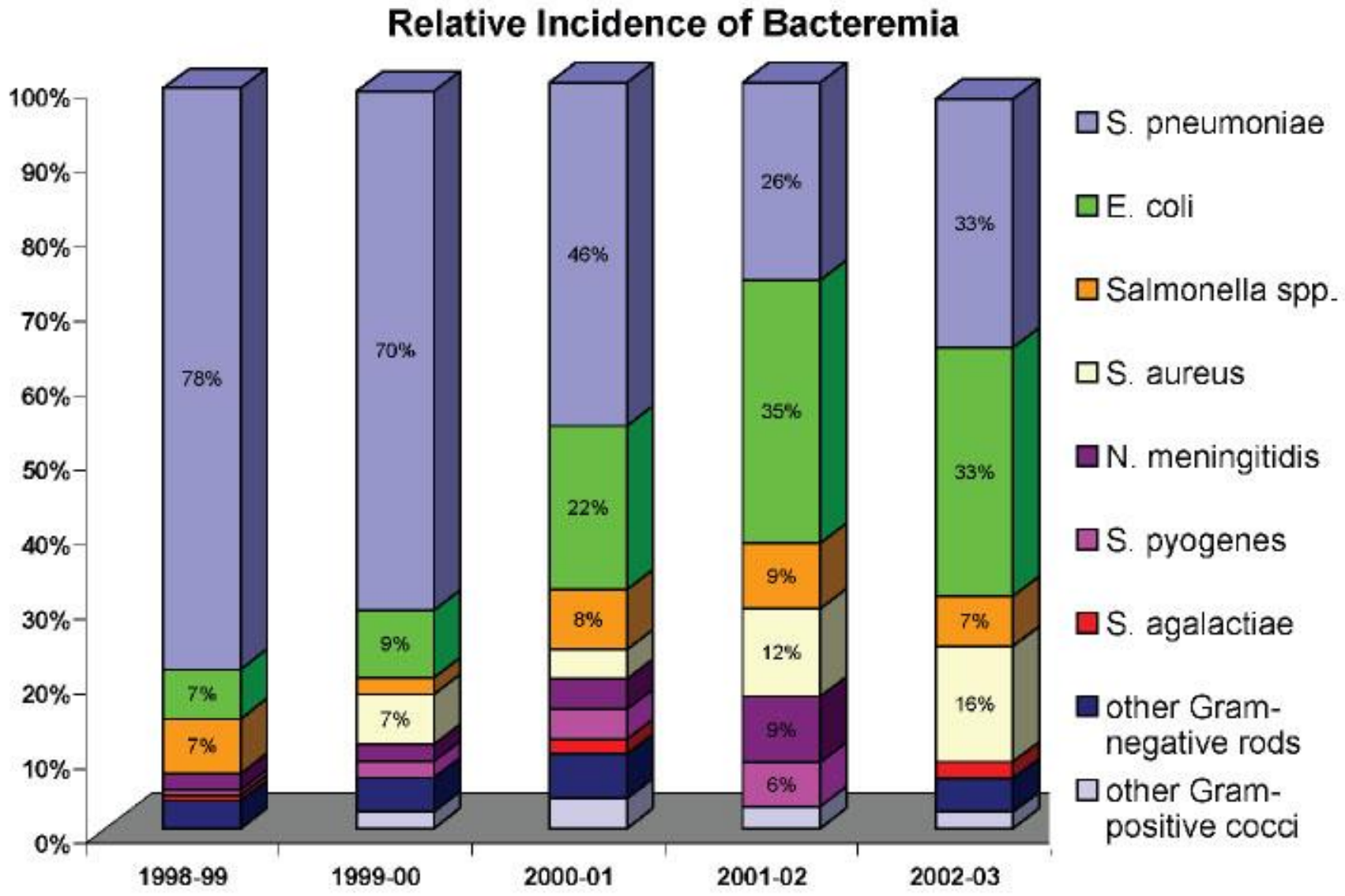
Streptococcus pneumoniae

Changing Epidemiology of Outpatient Bacteremia in 3- to 36-Month-Old Children After the Introduction of the Heptavalent-Conjugated Pneumococcal Vaccine

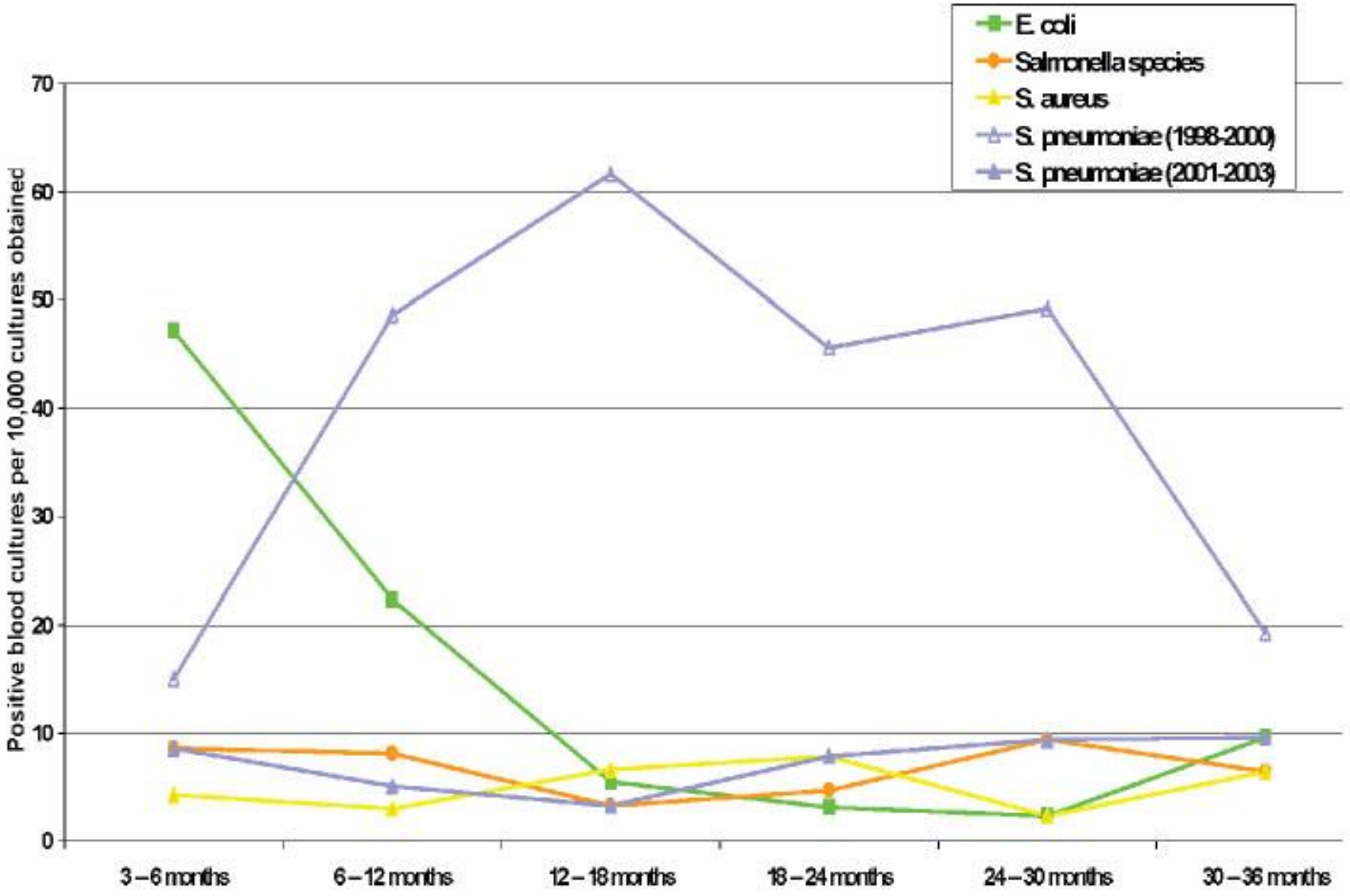
Arnd M. Herz, MD, Tara L. Greenhow, MD,† Jay Alcantara,* John Hansen, BA,‡ Roger P. Baxter, MD,§ Steve B. Black, MD,‡ and Henry R. Shinefield, MD‡*



(all absolute bacteremia rates ≥ 5/10,000 shown numerically in figure)



(all relative incidence values ≥ 5% shown numerically in figure)


E. coli
Salmonella species
S. aureus
S. pneumoniae (1998-2000)
S. pneumoniae (2001-2003)
Positive blood cultures per 10,000 cultures obtained
70
60
50
40
30
20
10
0
3 – 6 months
6 – 12 months
12 – 18 months
18 – 24 months
24 – 30 months
30 – 36 months

Current FWS

now <1% of children with FWS have bacteremia,

and risk of complications lower

badness rate <<1%

Blood Culture and Bacteremia Predictors in Infants Less Than Three Months of Age With Fever Without Source

Borja Gómez, MD, Santiago Mintegi, MD, Javier Benito, MD, Andere Egireun, MD, Diego Garcia, MD, and Eider Astobiza, MD

The Pediatric Infectious Disease Journal • Volume 29, Number 1, January 2010

TABLE 4. Risk of Bacteremia Related to Factors That Can be Assessed Before Performing a Blood Culture (Unadjusted)

Risk Factor	Positive Blood Culture	OR (95% CI)
Medical history		2.15 (0.68–6.29)
Not previously healthy vs	5/119 (4.2%)	
Previously healthy	18/899 (2.0%)	
General appearance		8.01 (2.76–23.05)
Not well-appearing vs	6/48 (12.5%)	
Well-appearing	17/970 (1.8%)	
Age		1.72 (0.66–4.39)
≤30 d vs	8/243 (3.3%)	
>30 d	15/775 (1.9%)	
Gender		2.13 (0.78–6.09)
Male vs	17/585 (2.9%)	
Female	6/433 (1.4%)	
Highest temperature detected		3.37 (1.16–9.36)
38°C–39.5°C vs	17/895 (1.9%)	
≥39.5°C	6/98 (6.1%)	
Urine dipstick*		3.70 (1.48–9.19)
Leukocyturia and/or nitrituria vs	10/178 (5.6%)	
Normal	13/822 (1.6%)	

Results are expressed as number (%).
*This information was not recorded for 9 patients.

Predicting Severe Bacterial Infections in Well-Appearing Febrile Neonates

Laboratory Markers Accuracy and Duration of Fever

Silvia Bressan, MD, Barbara Andreola, MD, Francesca Cattelan, MD, Tiziana Zangardi, MD, Giorgio Perilongo, MD, and Liviana Da Dalt, MD

The Pediatric Infectious Disease Journal • Volume 29, Number 3, March 2010

TABLE 1. Final Diagnosis of Patients With Severe Bacterial Infections (n = 25)

	No. Patients	%	Causative Organisms
Urinary tract infections (UTI)	15	60%	13 *Escherichia coli* 2 Enterococco 1 *Klebsiella pneumoniae*
Bacteremia	3	12%	3 group B Streptococcus
Bacteremia and UTI	2	8%	2 *Escherichia coli*
Meningitis	3	12%	3 group B Streptococcus
Pneumonia	1	4%	Not determined
Osteomyelitis	1	4%	Not determined

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TABLE 2. Laboratory Markers of Patients With and Without SBI for Initial (<12 h From Fever Onset), and Repeated Determination (>12 h From Fever Onset)

	SBI (n = 25)	Non SBI (n = 74)	*P*
<12 h from fever onset (99 patients)			
WBC (mm^3)	11130 (8600–13950)	9960 (7560–12500)	NS
ANC (mm^3)	6700 (4300–8040)	3670 (2600–5100)	<0.0001
CRP (mg/L)	16.1 (3.7–49.6)	1.8 (1.0–6.3)	<0.0001
	SBI (n = 5)	**Non SBI (n = 53)**	***P***
>12 h from fever onset (58 patients)			
WBC (mm^3)	21520 (10400–23220)	9980 (7150–11575)	0.0341
ANC (mm^3)	11580 (8600–15030)	3040 (2050–3870)	0.0104
CRP (mg/L)	55.3 (44.3–62.5)	3.5 (1.3–10.1)	0.0003

Data are expressed as median and interquartile range.
NS indicates non significant.

Interpreting Complete Blood Counts Soon After Birth in Newborns at Risk for Sepsis

AUTHORS: Thomas B. Newman, MD, MPH,[a,b] Karen M. Puopolo, MD, PhD,[c,d,e] Soora Wi, MPH, [b] David Draper, PhD,[f] and Gabriel J. Escobar, MD[b,g]

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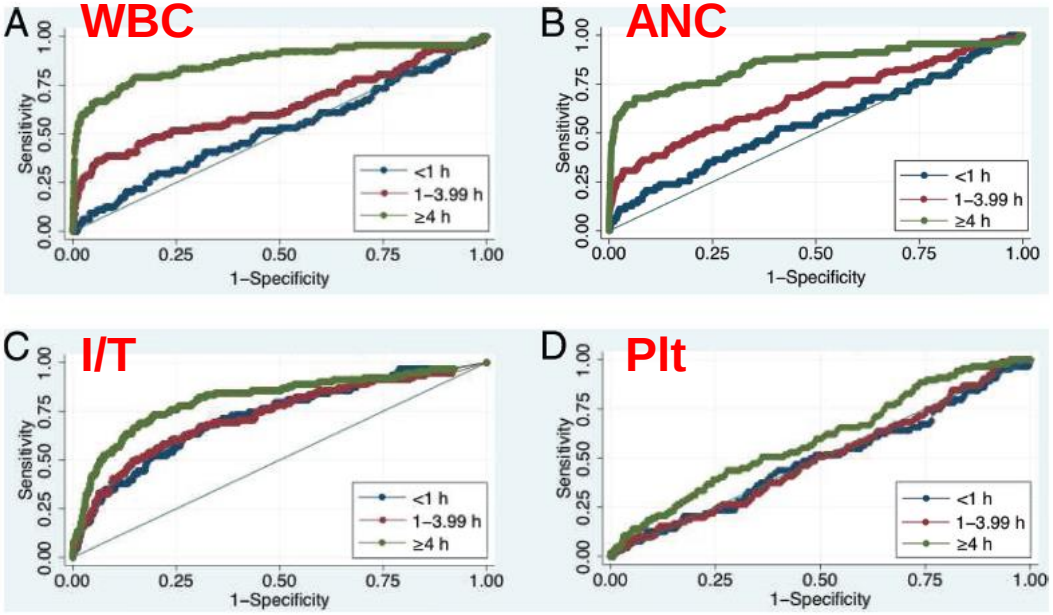

FIGURE 2

ROC curves for WBC counts (A), ANCs (B), I/T ratio (C), and platelet counts (D) performed at <72 hours according to age at the time of the CBC.

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Pediatrics 2010;126;903-909; originally published online Oct 25, 2010;
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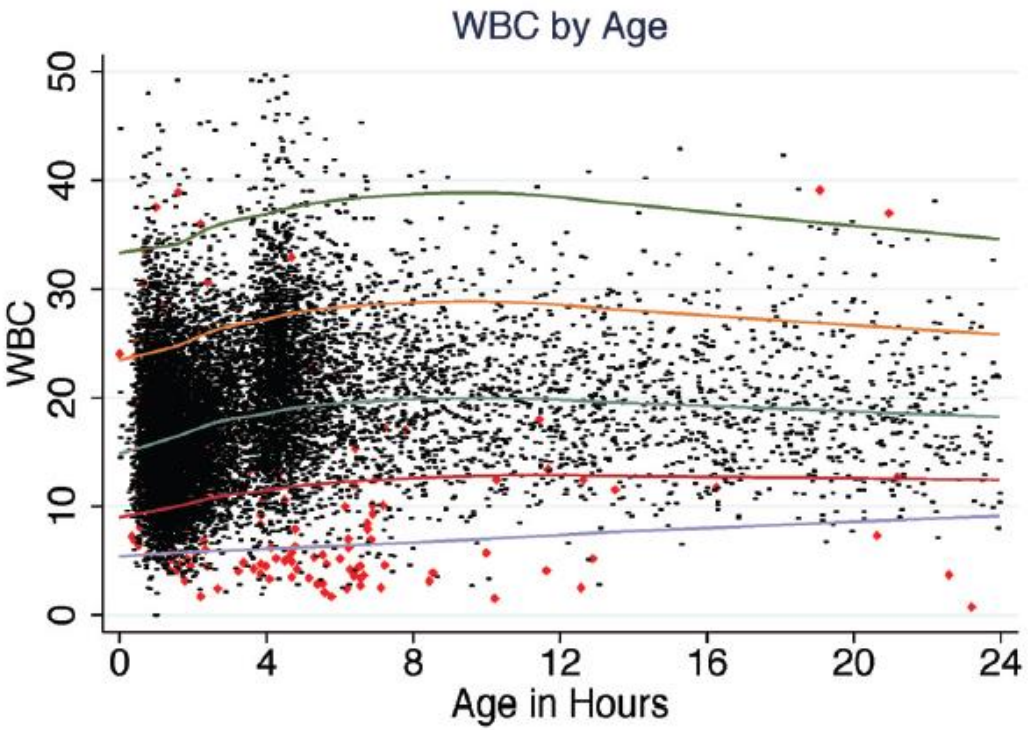

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FWS—Work-up

after careful H+P

for everyone

blood culture, CBC/D

OPEN ACCESS Freely available online

PLoS one

Changing Epidemiology of Serious Bacterial Infections in Febrile Infants without Localizing Signs

Kevin Watt[1], **Erica Waddle**[1,2], **Ravi Jhaveri**[1,2]*

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Table 2. Types of Serious Bacterial Infections in Early and Later periods.

	1997–2001	2002–2006	*p* value
SBI	20	52	0.001
%SBI	6.5%	14.4%	
UTI	13	45	0.0002
Bacteremia	7[a]	11[b]	0.54
Meningitis	1	2[c]	0.64

[a]one patient had UTI+Bacteremia.
[b]five patients had UTI+Bacteremia.
[c]one patient had Bacteremia+Meningitis.
doi:10.1371/journal.pone.0012448.t002

Table 4. SBIs by Age Group.

Age	1997–2001				2002–2006				
	SBI	UTI	Bacteremia	Meningitis	SBI	UTI	Bacteremia	Meningitis	*p* value-UTI
0–30 days	7[a]	4	3	1	9[b]	7	5	-	0.30
31–60 days	8	5	3	-	22[c]	18	6	1	0.01
61–90 days	5	4	1	-	21	20	-	1	0.02

[a]1 UTI was urosepsis.
[b]3 UTIs were urosepsis.
[c]2 UTIs were urosepsis, 1 meningitis had concomitant bacteremia.
doi:10.1371/journal.pone.0012448.t004

FWS—Work-up

after careful H+P

for girls <2yo, boys <6mo

(to 1yo if uncircumcised)

urine culture, U/A

FWS—Work-up

after careful H+P

if <3mo, if suspicion, if exposed

CSF culture, CSF analysis

FWS—Work-up

after careful H+P

consider a CXR

FWS—Empirical Tx

if work-up is unrevealing,

consider antibiotic therapy

FWS—Empirical Tx

consider antibiotic therapy if

- unsure of follow-up
- unsure of reliability
- no relationship with family

FWS—Antibiotics

ceftriaxone and daily follow-up

orals in select cases

FUO—Rational Work-up

patient should have already had

- blood culture, CBC/D
- urine culture, U/A
- CXR

FUO—Rational Work-up

what now makes the list of things that are common, or things that could kill you?

FUO—Rational Work-up

Rheumatology

send ESR, CRP

consider ANA

unless obvious disease,

I don’t push beyond this

FUO—Rational Work-up

Hematology/Oncology

repeat CBC + manual differential

send chemistries, including Ca and uric acid

call H/O, discuss BM

FUO—Rational Work-up

Infectious Diseases

- serial blood cultures (endocarditis)
- place PPD (tuberculosis)
- send viral studies
  (sinus, pharynx, stool, urine)
- send complement (CH50)

FUO—Rational Work-up

Infectious Diseases, p2

consider imaging

bone scan (osteomyelitis)

MRI (bones, joints)

CT (occult abscesses)

FUO—Rational Work-up

Infectious Diseases, p3

consider cardiology (Kawasaki)

consider unusual cultures / tests

Brucella, MOTT, *Bartonella*, *Francisella*, HACEK, *Mycoplasma*, etc.

FUO—Rational Work-up

Infectious Diseases, p4

every child getting an FUO w/u

should get HIV testing!!!

FUO—Rational Work-up

Infectious Diseases, p5

never forget STIs

send RPR, culture for GC, culture for *Chlamydia*

FUO—Rational Work-up

Infectious Diseases, p6

culture any site / fluid / tissue you can

FUO—Further Work-up

zebras are just that, uncommon

don’t send tests for unusual genetic disorders unless the history dictates it

FUO—Empirical Tx

in general,

NONE

FUO—Empirical Tx

we know that

1. most children will get better
2. most children have common illnesses
3. it hasn’t killed them yet!

FUO—Empirical Tx

giving antibiotics to a child with FUO, especially after it has been going on for a while, is like shooting a gun into a dark room

(please just send them to ID clinic)

Finally…

when is it too much?

my kid has a cold constantly…

my kid has had three pneumonias this year…

my kid has had pneumonia and meningitis and a joint infection…

Immune Deficiency

these are uncommon, but you will see them

never forget HIV!!!

and consider SCID, CGD, diGeorge, etc.

Immune Deficiency

context is everything

daycare? playmates?

family history? siblings?

underlying disorders?

past history?

Finally…

when is it too much?

my kid has a cold constantly…

(probably daycare)

Finally…

when is it too much?

my kid has had three pneumonias this year…

(worrisome, asthma?)

Finally…

when is it too much?

my kid has had pneumonia and meningitis and a joint infection…

(ain’t right)

Case 1

10 yo ♀ with recurrent fevers to 102˚ F daily for six weeks

- also has generalized malaise
- unusual rash on legs
- good workup by PMD
- family worried

Case 2

8 mo ♂ with third episode of pneumonia

- growth reasonable
- no FHx of recurrent illnesses
- CXR with multifocal infiltrates
- PMD worried

Case 3

5 yo ♀ with daily fevers increasing in height for four weeks

- some cervical lymphadenopathy
- tired look
- initial lab work normal
- weight curve has flattened

Final Word

Please call. Seriously.

We love this stuff.

Fellow pager 970-7420 (inpatient)
/ 970-7415 (outpatient)
consults / questions (24-7-365)

ID Emergencies in Pediatrics

13 June 2017
Tony Moody MD
Duke Pediatric Infectious Diseases

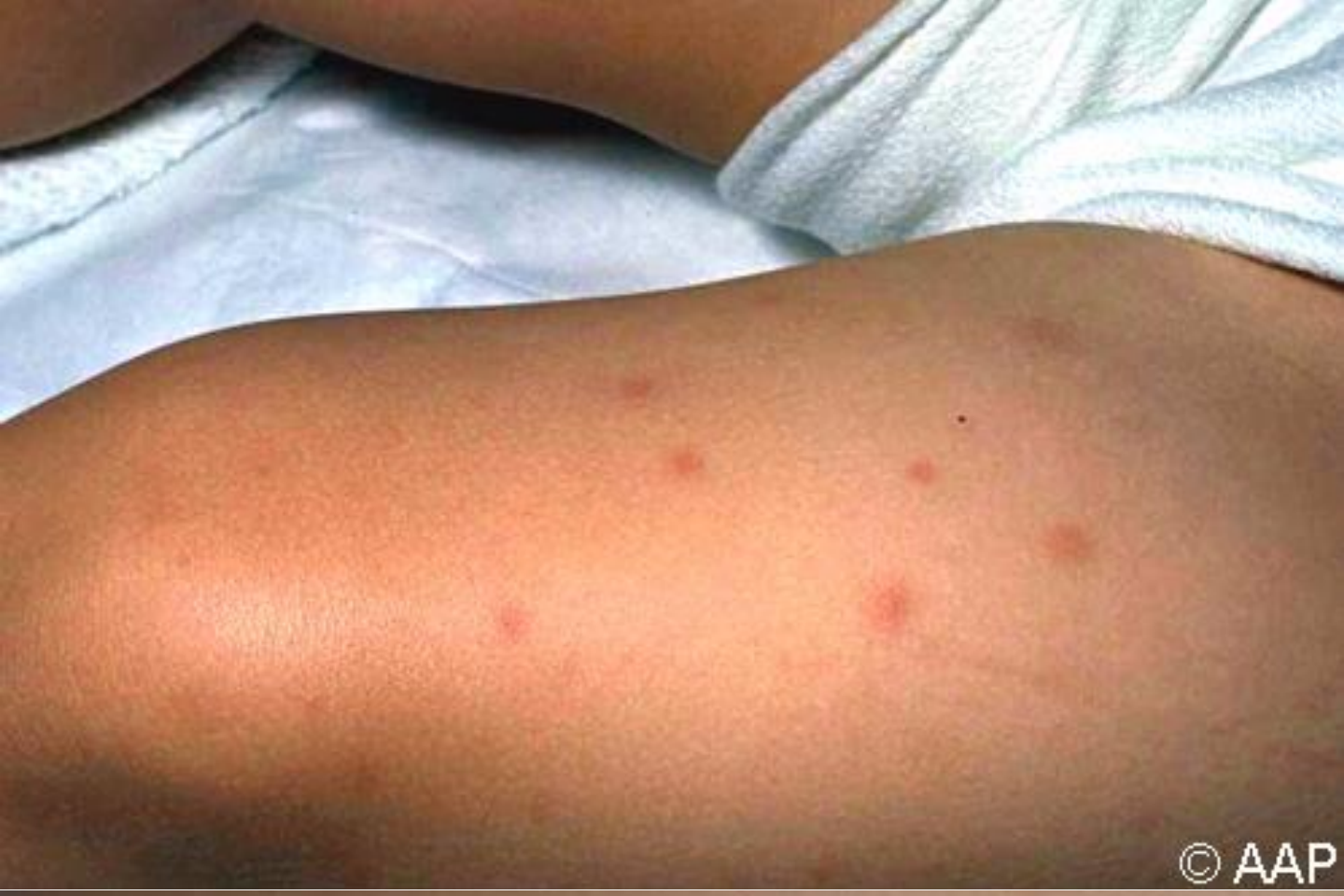
Goals

- discuss infections that can kill or maim without prompt attention

- outline presentation, labs needed, interventions needed

Case 1

You are in the ED on Wednesday, near the end of your shift. You are asked to eyeball an 11 mo ♂ with decreased feeding and urination, fever and lethargy, all with sudden onset. On exam you see a rash on with small, non-blanching, red macules with dark centers.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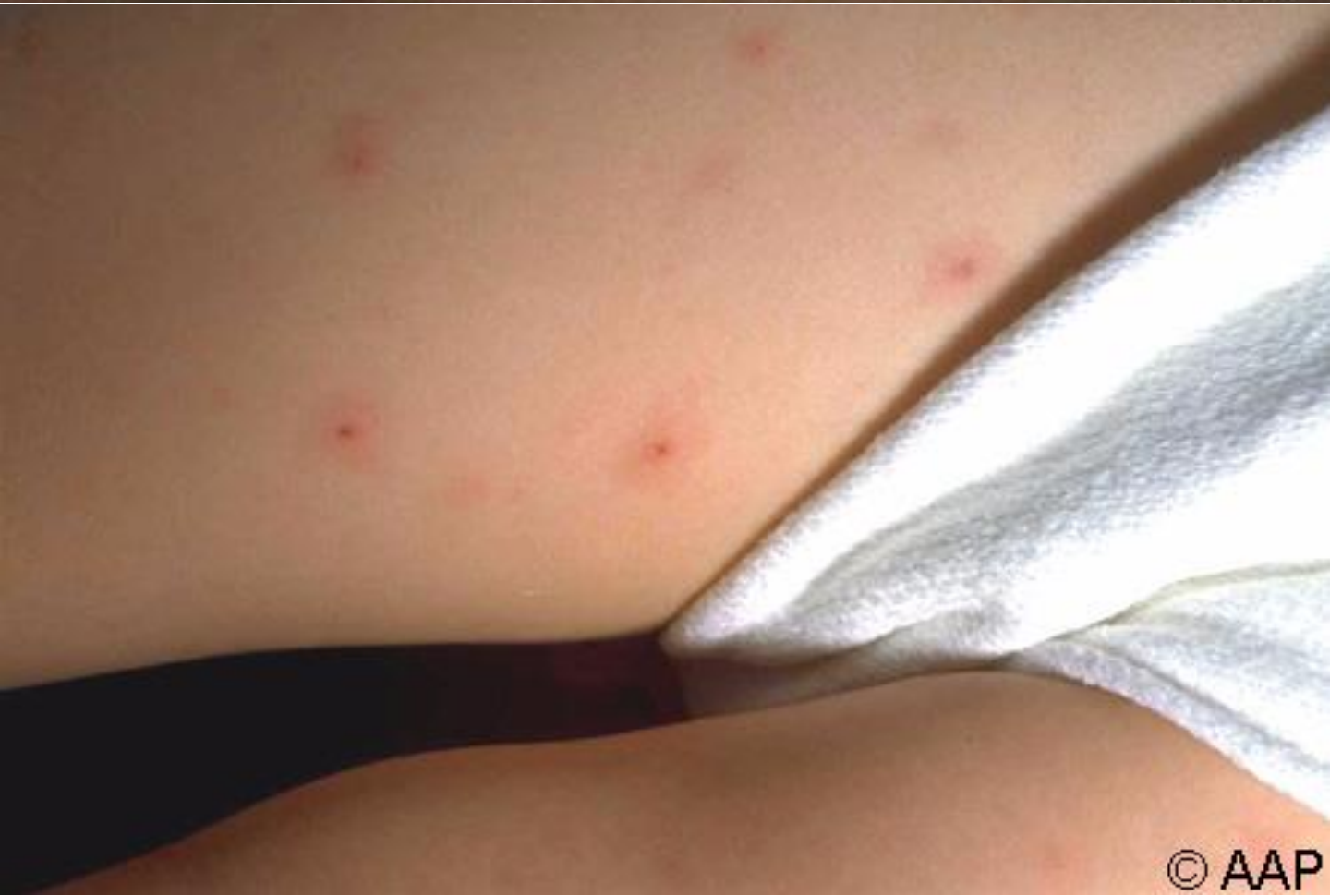
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Case 1

Your next action for this patient should be

A. diagnose a viral illness and discharge

B. obtain a blood culture

C. perform a lumbar puncture

D. administer ceftriaxone IM.

Case 1½

Children in his daycare room should

A. receive routine care

B. receive vaccination against pneumococcus

C. receive rifampin prophylaxis

D. have lumbar punctures performed.

Case 2

On Thursday, you see a 6yo ♀ with 3 days of fever & sore throat. Her mother reports a red, raised rash. You find HR 120, T 39. Her L leg below the knee is swollen. She is crying and inconsolable.

Case 2

Your next action for this patient should be

A. LA Bicillin for strep throat

B. start oral penicillin

C. start IV penicillin and clindamycin

D. call for a surgical consult.

Case 3

On Friday, you see a 20mo ♀ with a 2 day history of fever & fussiness. Her mother notes the child is refusing to walk and is fussy with diaper changes. You see a child with T 38.5 and holding her R leg flexed and externally rotated.

Case 3

Your next action for this patient should be

A. call for an orthopedic consult

B. call radiology for a hip ultrasound

C. start meropenem

D. diagnose toxic synovitis and discharge on NSAIDs.

Case 4

On Sunday, you see a 5yo ♂ with 3-4 days of congestion / rhinorrhea. This morning his mother noted the acute onset of R eye swelling. On exam you see tense edema of the eyelid with proptosis, lateral gaze paralysis, conjunctival injection.

Case 4

Your next action for this patient should be

A. IVIG infusion

B. Call ENT / Ophtho

C. start 3rd generation cephalosporin

D. thyroid studies.

Case 5

On Monday, you see a 2yo ♂ whose family are recovering from a “flu-like” illness. He had been recovering until this morning when he developed a distressed look and high fever. On exam he has inspiratory stridor, retractions, and a normal O_2 saturation.

Case 5

Your next action for this patient should be

A. Immediate intubation

B. CXR

C. Chest CT

D. administer nebulized albuterol.

Case 5½

The CXR is shows no foreign body, little parenchymal disease. Now

A. Immediate intubation

B. start vancomycin

C. Chest CT

D. administer nebulized albuterol.

Case 6

In 1985, you see a 3yo ♀ who had mild fever and cough followed by the sudden onset of respiratory distress and irritability. She is hoarse, sitting in mother's lap, leaning forward, drooling, and has retractions.

Case 6

Your next action for this patient should be

A. Immediate intubation by the intern

B. CXR

C. immediate intubation by an anesthesiologist

D. start an IV for antibiotics.