AMERICAN COLLEGE OF EMERGENCY PHYSICIANS
SCIENTIFIC ASSEMBLY
1999

Cost-Effective Management of Common Infections

How often does the emergency physician treat a case of pharyngitis or cervicitis or evaluate a febrile child at risk for occult bacteremia? How do we balance the potential costs and benefits of therapeutic and diagnostic options for these patients? Through case presentations, the lecturer will discuss how cost-effective analysis can help us to approach these "bread-and-butter" cases.

- Discuss the place of rapid streptococcal screen, throat culture, and treatment indications for acute pharyngitis in the varied hospital setting.
- Discuss the value of laboratory testing and empiric antibiotic therapy in the evaluation and treatment of the patient with cervicitis.
- Discuss the role of the leukocyte count, blood cultures, and empiric antibiotic treatment for febrile children at risk for occult bacteremia.

MO-16
Monday, October 11, 1999
9:00 AM - 9:55 AM
Room # N208
Las Vegas Convention Center

FACULTY

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Cost Effective-Treatment of Common Infections

Is there evidence for what we do?

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Questions

- What is the risk of occult bacteremia in well appearing infants with fever'?
- Do empiric antibiotic? improve outcomes?
- Arc parenteral antibiotics superior to oral?
- Do clinical and laboratory parameters help stratify patients into different risk groups'?

Number Needed to Treat (NNT)

- Number of patients you need to treat to prevent one additional outcome of interest
- Calculated as inverse of absolute risk reduction (ARR) = 1/ARR
- ARR is the difference between event rates in the control group and treatment group

Threshold NNT (T-NNT)

- The NNT at which treatment benefit is balanced by adverse effects and costs of treatment strategy
- T-NNT=1/(Vae1 x Rae1)+(Vae2 x Rae2).
  - Vae = relative *Value* of adverse event
  - Rae = *Rate* of the adverse event
  - Costs can be included, formula very complex

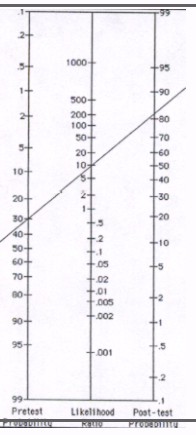
NNT

- If Rx-NNT falls below T-NNT, favors Rx
- If NNT's overlap, recommendations weak
- If Rx-NNT above T-NNT, favors NO Rx

Likelihood Ratio (LR)

- Likelihood of a given test result in patient's with disease compared to the same test result in patients without disease
- Allows direct estimate of post-last disease probability for a given test result

Fagan Nomogram



Pediatric Fever Practice Guideline

- Infants 0-90 days
  - All get fever work up
- Infants 3-36 Mo
  - Toxic appearing - admit
  - Temp> 39 C
    - CBC, UA, CXR, Stool Cx, Blood Cx, LP
    - Empiric antibiotics

Baraff, et al. *Ped Inf Dis J.* 1993;12:389-94

Incidence of Occult Bacteremia

Study/yr	# Patients	% Pos Cx	S. Pneum	H. flu	N. Menin	Salm
Jaffe 87	955	2.8	85%	7.4%	0%	7.4%
Fleisher 94	6680	3	85%	4.7%	0%	3.6%
Harper 95	559	NA	84%	6%	2%	7%
Lee 98	9465	1.6	92%	0%	1%	5%
Haddon 99	534	3.4	83%	0%	11%	0%

Antibiotic Therapy

- Does antibiotic therapy improve *outcome* in patients with occult bacteremia'?

Persistent Bacteremia

Author/Yr	Antibiotics	No Antibiotics	OR/RR
Jaffe 1987	5.3%	12.5%	0.42
Baraff 1992	4%	21%	0.2
Harper 1995	6% oral 0% IM	27%	0.22 0

Serious Bacterial Infection

Author/Yr	Antibiotics	No Antibiotics	OR/RR
Jaffe 1987	10.5%	12.5%	0.84
Harper 1995	10% oral 6% IM	35%	0.29 0.17
Rothrock 1997	3%	9.7%	0.34

Meningitis

Author/Yr	Antibiotics	No Antibiotics	OR/RR
Baraff 1992	4.5%	9.2%	0.49
Baraff 1993	8.2% oral 0.3% IM	9.8%	0.84 0.03
Harper 1995	2.6% oral 1.4% IM	2.3%	1.1 0.61
Rothrock 1997	0.8%	2.7%	0.30

Is the Benefit Worth It?

- 'Threshold-NNT
- 1 / (Vae1 x Rae1) + (Vae2 x Rae2) …
- Adverse events
  - GI side effects 2.1-5.7%, some 19%
  - Dermatologic 2.7%
  - Anaphylaxis 0.004% oral, 0 04% IV
  - Death 0.001-0 002%

Meningitis

- Threshold NNT = 58-217
- Treatment NNT = 21-111
  - NNT overlaps threshold for all meningitis
- For *S. Pneumo* NNT = 52-76
  - NNT overlaps threshold for *S. Pneumo* meningitis
- Unclear if strategy favors empiric Abx

Persistent Bacteremia

- 'Threshold NNT = 27-83
- Treatment NNT = 5-27
- For the outcome of PB, strategy favors empiric antibiotic therapy

Serious Bacterial Infection

- Threshold NNT = 46-154
- Treatment NNT = 5-50
- For the outcome of SBI, treatment NNT overlaps threshold NNT
  - Strategy may favor empiric antibiotics, strength of recommendation is not as strong

Risk Stratification

- For persistent bacteremia evidence favors empiric Rx
- For all types of meningitis, and SBI strategy favors further risk stratification
- Is it possible to further risk stratify patients?

WBC Count

WBC	Sens %	Spec %	LR pos	LR neg	PsTP +	PsTP -
≥ 5	100	6	1.06	0	3%	0.1%
≥ 10	98	44	1.75	0.045	4%	0.15%
≥ 15	86	77	3.74	0.18	9%	0.5%
≥ 16	77	81	4.05	0.33	10%	0.7%
≥ 17	72	84	4.5	0.32	11%	0.7%
≥ 18	64	87	4.9	0.41	12%	1%
≥ 19	56	90	5.6	0.48	13%	1.2%
≥ 20	48	92	6	0.57	14%	1.5%

Lee, et al. *Arch Ped Adol Med.* 1998;152:624-628

WBC Count

- Alternate approach
- Lose discriminatory power when continuous data is dichotomized
  - Arbitrary cutoff point

  Intuitive difference between WBC 15. I and 25
- Look at discrete intervals instead

WBC Count

WBC	Cx pos	Cx neg	LR	PsTP
0 – 5	0	543	0	0.1%
5 – 10	3	3291	0.06	0.2%
10 – 15	15	2767	0.36	1%
15 – 20	48	1337	2.4	6%
20-25	34	469	4.9	12%
25-30	12	155	5.3	14%
30-50	15	67	15.2	28%

Lee, et al. *Arch Ped Adol Med.* 1998;152:624-628

WBC Count

- Elevated WBC count increases risk OB
- Traditional cutoff of 15.000 arbitrary
- Use interval approach instead of cutoff
- WBC 15-20, probably empiric antibiotics
- WBC above 20, strategy favors antibiotics

Antibiotic Therapy

- What antibiotic option works best?

Serious Bacterial Illness

Author/yr	# Patients	Oral	Parenteral	OR/RR
Fleisher/94	6680	5/91(**5.6%**)	3/101(**3%**)	0.43
Harper/95				
All bacterem	461	46/461(**10%**)	28/461(**6%**)	0.6
S. Pneumo	382	23/382(**6%**)	19/382(**5%**)	0.83

Meningitis

Author/yr	# Patients	Oral	Parenteral	OR/RR
Fleisher/94	6680	3/91(**3.3%**)	2/101(**2%**)	0.61
Harper/95				
All bacterem	461	12/461(**2.6%**)	6/461(**1.4%**)	0.54
S. Pneumo	382	4/382(**1%**)	3/382(**.78%**)	0.78

Persistent Bacteremia

Author/yr	# Patients	Oral	Parenteral	OR/RR
Fleisher/94	6680	NA	NA	NA
Harper/95				
All bacterem	461	28/461(**6%**)	0/461(**0%**)	0.0
S. Pneumo	382	8/382(**2%**)	0/382(**0%**)	0.0

SBI for Bacteremia

- All bacteremia
  Threshold NNT = 268
  - Treatment NNT = 25-38
- *S Pneumo* bacteremia
  - Threshold NNT = 268
  - Treatment NNT = 100
- Strategy favors parenteral antibiotics

Meningitis

- All meningitis
  - Threshold NNT = 350
  - Treatment NNT = 77-83
- S. *Pneumo* meningitis
  - Threshold NNT = 350
  - Treatment NNT = 100
- Strategy favors parenteral antibiotics

Persistent Bacteremia

- All persistent bacteremia
  - Threshold NNT = 147
  - Treatment NNT = 17
- *S. Pneumo* persistent bacteremia
  - Threshold NNT = 147
  - Treatment NNT = 50
- Strategy favors parenteral antibiotics

Cervicitis

- What is the prevalence of gonorrheal or chlamydial cervicitis?
- What is the benefit of treating of cervicitis?
- Is diagnostic testing necessary?
- Which regimen is most cost effective'?

Prevalence of Cervicitis in ED

- Approximately 1:4 ratio of GC to chlamydia in patients with vaginal d/c
- Prevalence of GC reported between 3-9%
- Prevalence of chlamydia 13-40%
- 13% of patients with chlamydia have GC
- 30% of patients with GC have chlamydia

Outcomes of Cervicitis

- Upper tract infection (PID)
- Chlamydia cervicitis
  - 25-40% risk of developing PID
  - RRR of 75% with treatment
- GC cervicitis
  - 15-20% risk of developing PID
  - RRR of 90% with treatment

Cates, W. *Epidem Rev.* 1990;12:199-214

Outcomes of PID

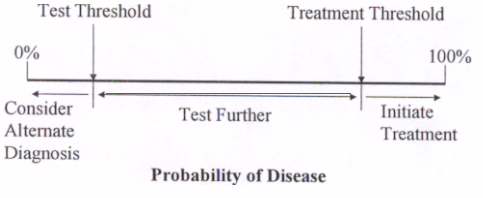
1

- Infertility
  - GC PID: risk of infertility at least 5%
  - Chlamydia PID: 11% risk infertility after 1 episode of PID, 23% after 2, 54% after 3
- Ectopic pregnancy, pregnancy complications
  - GC PID: 9% risk of developing ectopic
  - Chlamydia PID: 7-8% risk of ectopic

Cates W, Wasserheit JN. *Amer J Ob Gyn.* 1991;164:1771-81

- How certain do you need to be that a patient has cervicitis to initiate empiric treatment?
- What are your *treatment and test thresholds?*

Decision Making Thresholds



Thresholds for Cervicitis

- 'Treatment threshold
  - 50.60%
- Test threshold
  - 5%

Clinical Criteria

- Age less than 25, unmarried
- Multiple sexual partners past year
- Cervical discharge
- Absence of recent antibiotic use
- Clinical signs of PID

Magder, LS. *Am J Epidem. 1988;128:298-308*

Clinical Criteria

- If more than 4 of these criteria present, the probability of cervicitis is > 60%
  Treat empirically for GC and Chlamydia
- If 1 or less, probability of cervicitis is < 5%
  Consider other causes for vaginal discharge
- If 2-3 criteria present test further

Magder, LS. *Am J Epidem. 1988;128:298-308*

Diagnostic Test Options

- Cervical gram stain
- Cervical culture
- DNA probe, amplified DNA probes
  Ligase, polymerase chain reactions
- Direct fluorescent antibody
- Enzyme immunoassay

Diagnostic Tests for Gonorrhea

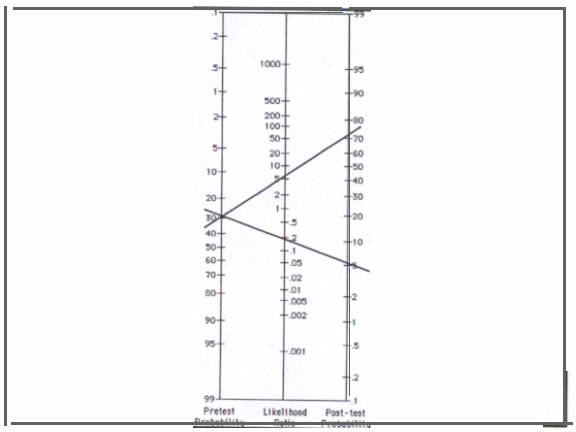
Test	Sens(%)	Spec(%)	LR Pos	LR Neg
Gram stain	50-79	>90	5-8	0.2-0.6
Culture single swab	85-90	98	45	0.15
DNA probe	90	96	23	0.10

Diagnostic Tests for Chlamydia

Test	Sens(%)	Spec(%)	LR Pos	LR Neg
Cell culture single swab	70-80	98	35-40	0.2-0.3
DNA probe LCR, PCR	>95	99	95	0.05
Fluor Ab	70-87	97-99	23-87	0.13-0.3
Enz IA	80-85	98	40-43	0.20

Gonorrhea

- For Gonorrhea, results of cervical gram stain will often raise or lower posttest probability above or below thresholds



Chlamydia

. In the ED, if testing is necessary, rapid diagnostic tests are preferred

- Amplified DNA probes (LCR/PCR) have highest accuracy

  Strategy of selective testing using most accurate method is suggested

1998 CDC Guidelines

- Results should be based on Cx or DNA test
- Empiric Rx for populations at high risk
- Chlamydia
  - Azithromycin 1 gm oral/Doxy 100 mg bid 7d
- Gonorrhea
  - Cefixime 400 mg oral/Ceftriaxone 125 mg IM

Bacterial Eradication

- Ceftriaxone - 99%
- Cefixime - 97%
- Adthromycin - 97%
- Doxycycline - 99%

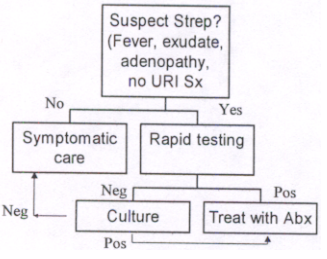
Medication Cost

- Ceftriaxone 125 mg $8.60
- Cefixime 400 mg - $4.67
- Doxycycline 7d - $5.5 I
- Azithromycin I gm - $18.75
- Cart-cffeciivc analyses suggest single dose therapy when compliance is an issue

Epidemiology of Pharyngitis

Organism	Peds 4-12 (%)	Adults
Bacteria total	**30-36**	**8-15**
GAS	30-36	8-15
Other strep	0-3	0-18
N. Gonorrhea	0-0.01	0-0.1
A. Hemolyticum	0-0.05	0-10
M. Pneumoniae	0-3	0-10
C. Pneumoniae	0-3	0-9
Viral	15-40	30-60
Idiopathic	20-55	30-65

ID Society Practice Guideline



- Why not just treat everyone who comes into the ED for a sore throat with antibiotics?
  - What is the Threshold-NNT?

Outcomes for Strep Pharyngitis

- Non suppurative
  - Acute rheumatic fever
  - Post streptococcal glomerulonephritis
- Suppurative
  - Acute OM, acute sinusitis
  - Peritonsillar abscess
- Symptom relief

Adverse Outcomes of Treatment

- GI side effects
- Dermatologic
- Anaphylaxis
- Death
- Development of resistance organisms

Acute Rheumatic Fever

Group	Risk ARF Un Rx(%)	Risk ARF Rx(%)	ARR	RRR	NNT
U.S.	0.064	0.0179	0.0016	72%	**2170**
Aborigine	0.861	0.241	0.0062	72%	161
Strep Epidemic	3	0.84	0.022	72%	46

Acute Rheumatic Fever

- U.S. Threshold NNT varies from 370-830
. Treatment NNT = 2 170
- Does NOT favor a strategy of empiric antibiotic Rx in order *to prevent ARF*
- High risk population (Australian Aborigine) treatment NNT lower (161)

Favors empiric Rx

Suppurative Complications

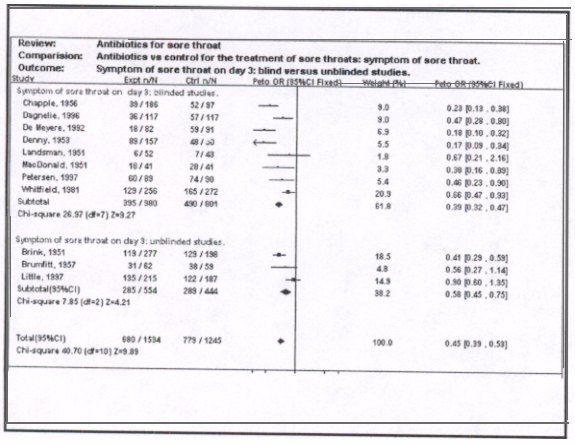
Group	Risk ARF Un Rx(%)	Risk ARF Rx(%)	ARR	RRR	NNT
Supp Compl	1-3.2	0.35-0.8	0.007-0.024	56%-73%	**42-154**

Suppurative Complications

- Threshold NNT varies lion, 35-93
- Treatment NNT varies from 42- I54
- Thresholds overlap. weak recommendation for empiric antibiotics in order to prevent suppurative complications of pharyngitis

Symptom Reduction

Group	Risk ARF Un Rx(%)	Risk ARF Rx(%)	ARR	RRR	NNT
Persist ST	63	44	0.19	71%	**5**



Symptom Reduction

- Threshold NNT = IO
- Treatment NNT = 5
- Favors antibiotic treatment strategy in order to reduce symptoms of pharyngitis

Clinical Criteria

- Can clinical criteria be used to effectively risk stratify patients?

Suggested Thresholds for Pharyngitis

- Probability of GAS pharyngitis is <5%
  - No test. no treatment
- Probability of GAS is 5-40%
  - Test further
- Probability of GAS is >40-50%
  Treat, "0 test

Cost-Effective Analyses

- Multiple cost-effective analyses have supported a similar approach
  - Lieu, TA. *Pediatrics.* 1990;85:246-256
  - Cebul, RD. *JAMA.* 1986;256:353-3357
  - Tompkins, RK. *Ann Int Med.* 1977;86:481-492
- Some even lower probability of GAS pharyngitis threshold to 20-30%, above which empiric antibiotic RX is felt to be cost effective

Clinical Criteria

- Dozens of scoring systems for sore throat
- 4 consistently high yield findings:
  - *Temperature > 38 degrees C*
  - *Tonsillar swelling/exudate*
  - *Tender anterior cervical adenopathy*
  - *Lack of cough/URI findings*

Clinical Criteria for GAS

# Findings	Prevalence Age 3-14(%)	% in categ Age 3-14	Prevalence Adult(%)	% in categ Adult
0	< 1	< 1	2-3	39
1	12.5	9	4-6	31
2	21	21	9	19
3	29	26	27	7
4	51	43	57	4

Clinical Criteria for GAS

Risk Group	# Findings	Strategy	% in categ Age 3-14	% in categ Adult
Low	0	No test, No Rx	2	39
Intermediate	1-3	Test	56	57
High	4	Rx, No test	42	4

Testing for Pharyngitis

- Culture
- Rapid antigen detection tests (RADT)
- Optical immunoassay
- DNA probes
- In ED, if follow up is unreliable, rapid testing is preferred

RADT

- Sensitivity (when used correctly) of 76-87%
- Specificities range from 90-96%
- In ED, sensitivities may range 45.55%
- LR positives range 5-17
- LR negatives range 0.16-0.6

OIA, DNA Probes

- Accuracy reported very similar to throat Cx
- Still more expensive

Which Antibiotic is Preferred?

- Many antibiotics eradicate strep better but..
- . In virtually every cost-effective analysis done. PCN (oral or IM) comes out on top
  - No resistance yet for *S. Pyogenes*
  - Erythromycin for Pen allergies
- Penicillin is the only antibiotic for which prevention of ARF has been demonstrated

Problems

- Assume that the presence of GAS in the pharynx of symptomatic patients defines GAS pharyngitis
- Eradication of GAS prevents sequelae
- Throat Cx is criterion standard to diagnose GAS pharyngitis and a patient that will benefit from antibiotic therapy

GAS Carrier State

. Up to 20% of asymptomatic individuals will have GAS on culture

May be higher in pediatric patients

- How do you distinguish a carrier with viral pharyngitis from bona fide GAS infection?
- Is throat culture an appropriate standard')

Throat Culture

- Tonsillar surface swab may not indicate real infective flora deep in tonsillar crypts
- Throat culture may be insensitive
  - Compared to ASO titers throat Cx under estimates infection by 42%, specificity 70%
  - Compared to multiple throat cultures, single swab has sensitivity of 85%

Antibiotics for Acute Sore Throat

- Argues for an *empirical* approach rather than microbiologic approach
- Based on outcome data. not testing
- 1998 Mcta-analysis from Cochrane
- 22 randomized, placebo controlled trials for acute sore throat regardless of etiology

Del Mar CB, Glasziou PP. Cochrane Collaboration. 7 Mav 1998

Antibiotics for Acute Sore Throat

- 10,484 cases of acute sore throat
- Treated compared to controls
  - ARF: RR = 0 28 (0.19-0 4)
  - AOM: RR = 0 23 (0.1-0.45)
  - Sx ST @ 3d: RR = 0.39 (0 32-0.47)
  - HA @ 3d: RR = 0.40 (0 28-0 56)
  - Fever @ 3d: RR = 0 56 (0.41-0 76)

Antibiotics for Acute Sore Throat

- Treatment hcnefit is clear hut...
- Should all patients he treated to realize this benefit to antibiotic therapy?
  - What is the magnitude of treatment effect?

Antibiotics for Acute Sore Throat

- Treatment NNT overlapped or were above Threshold NNT for all outcomes except Sx
- Symptom relief from antibiotics seen at 3d
  - Mean absolute duration of Sx shortened by half a day at 3 days from onset of Sx
  - 90% of both treated and untreated groups asymptomatic at 1 week

- Is this enough to recommend empiric antibiotic therapy for all patients with acute sore throat?

Ultimately, the most Cost-Effective Approach?

- You and your patient need to decide
- Stratify risk based on clinical parameters
- Avoid expensive testing
- Give the patient the facts
  - Magnitude of treatment effect on outcomes
  - Risks of treatment
- Let them decide if Rx is worth it to them