Choosing Antibiotics for Pediatric Acute Infections

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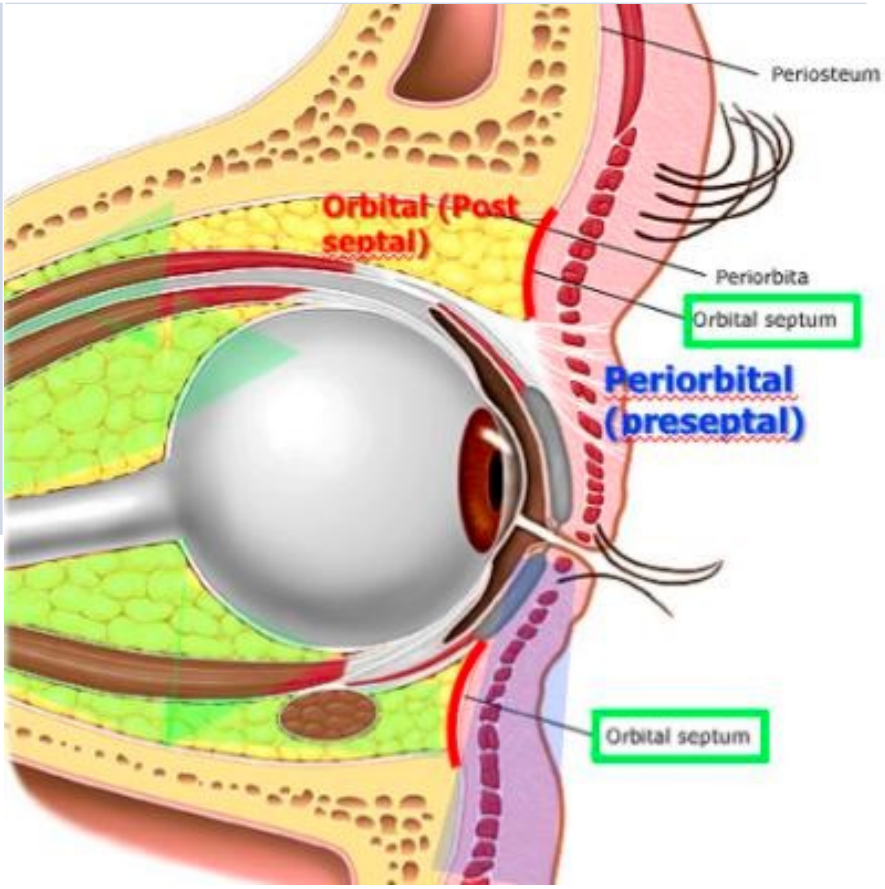
2/12/19

Objectives

- Understand and apply common principles of appropriate antibiotic use
- Understand how an ID specialist approaches clinical decision-making
- Describe basic pharmacology and spectrum of commonly used antibiotics

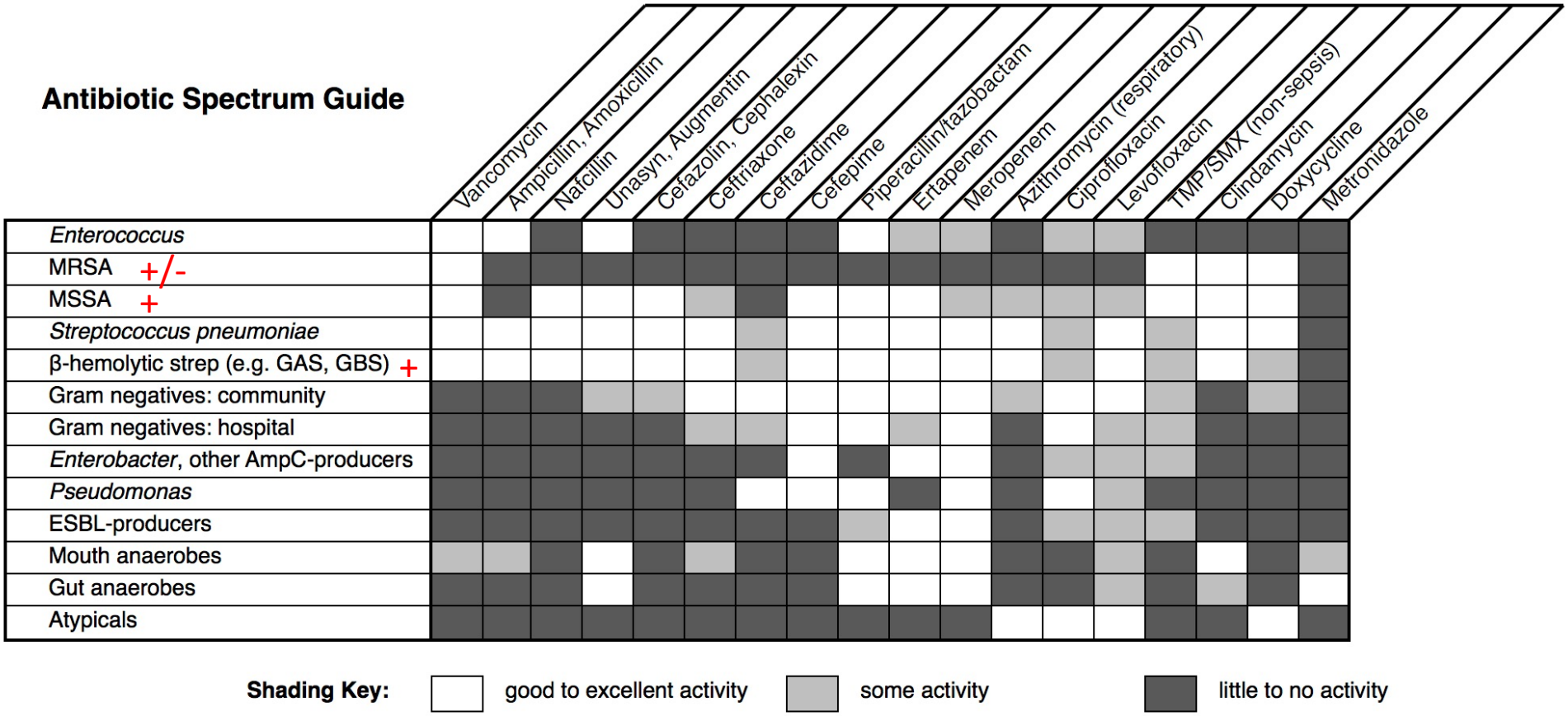
How to approach cases like an ID specialist?

Key Questions	Example
1. What is going on with this patient? *The Clinical Syndrome* *--What is the location?* *--How does infection develop (where do the pathogens come from?)* *(e.g. contiguous, hematogenous, etc.)* *--Something anyone can get vs. special host susceptibility?*	

Key Questions	Example
1. What is going on with this patient? *The Clinical Syndrome*	Preseptal/periorbital cellulitis Most commonly develops from contiguous extension of cutaneous focus – e.g. injury, chalazion, bite, etc. May develop from contiguous extension of sinusitis
2. What pathogens cause this clinical syndrome? *The Microbiologic Differential*	[redacted]

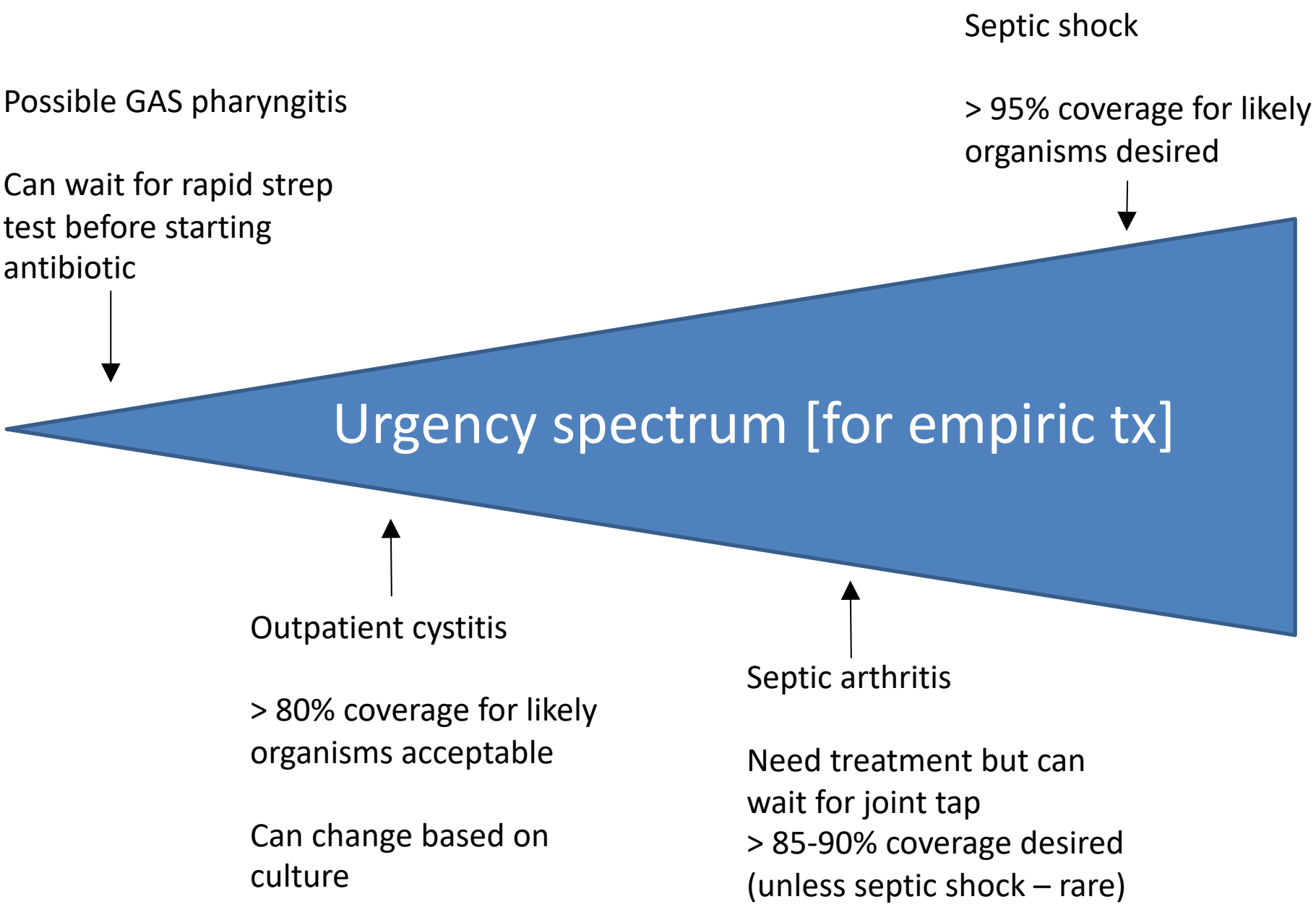
Key Questions	Example
1. What is going on with this patient? *The Clinical Syndrome*	Preseptal/periorbital cellulitis
2. What organisms cause this clinical syndrome in this type of patient? *The Microbiologic Differential*	Skin flora – *Staphylococcus aureus,* group A streptococcus most common Less common – etiologies of sinusitis – *Streptococcus pneumoniae, Staphylococcus aureus, H. influenzae, Moraxella,* anaerobes
3. What antibiotic(s) work against this organism in this condition? *Therapy Options* *--is it known to be active?* *--does it distribute to the site at sufficient levels?* *--has it been used successfully to treat the clinical condition?*	

Antibiotic Spectrum Guide



https://idmp.ucsf.edu/antibiotic-spectrum-guide

Key Questions	Example
1. What is going on with this patient? *The Clinical Syndrome*	Preseptal/periorbital cellulitis
2. What organisms cause this clinical syndrome in this type of patient? *The Microbiologic Differential*	Skin flora – *Staphylococcus aureus,* group A streptococcus most common Less common – etiologies of sinusitis – *Streptococcus pneumoniae, Staphylococcus aureus, H. influenzae, Moraxella,* anaerobes
3. What antibiotic(s) work against this organism in this condition? *Therapy Options*	Many antibiotics active against *Staphylococcus aureus* + group A strep Some active against MRSA Some active against respiratory Gram negatives
4. What is the margin of error for initial choice of therapy? *--How sick is this patient?* *--What might happen if initial therapy is not active? (Bad outcome likely/unlikely)* *--Is there diagnostic uncertainty?*	


Septic shock
> 95% coverage for likely organisms desired
Possible GAS pharyngitis
Can wait for rapid strep test before starting antibiotic
Urgency spectrum [for empiric tx]
Outpatient cystitis
> 80% coverage for likely organisms acceptable
Can change based on culture
Septic arthritis
Need treatment but can wait for joint tap
> 85-90% coverage desired
(unless septic shock – rare)

The Goldilocks Rule of Empiric Antibiotics

Too narrow:

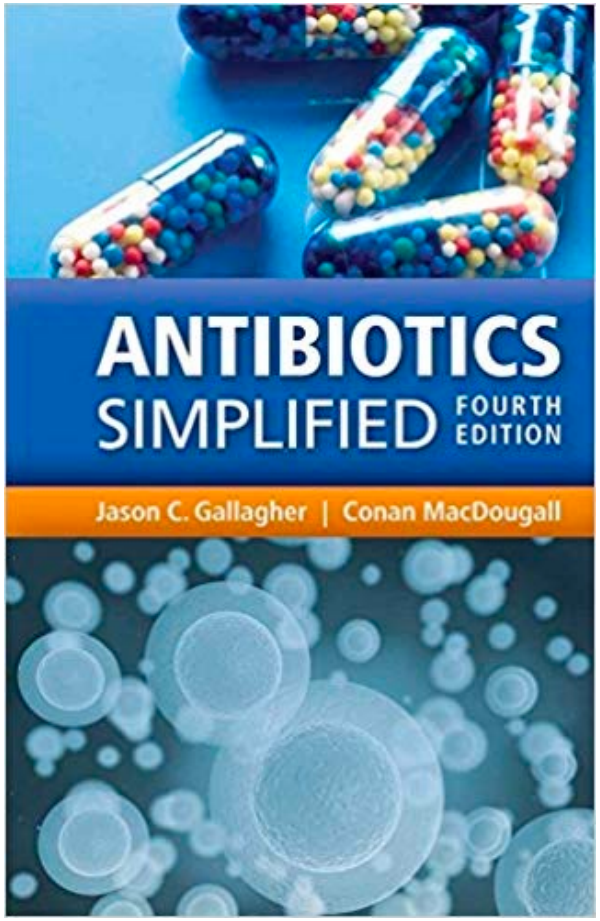
- May not be active against the causative organism --> failure of treatment
- Narrower ≠ less effective as long as organism is susceptible (often narrower agents are more effective)

Too broad:

- Collateral damage to the patient by eliminating important normal flora, causing *C. difficile*, resistance developing in the patient that can then be passed on to others

When options have equivalent efficacy, narrower and shorter treatment is ideal

Favorite Resources



Really good book to learn antibiotics + spectrum, & basic clinical microbiology

Dosing: Lexi-Comp

Adjustment for renal failure & dialysis:
https://kdpnet.kdp.louisville.edu/drugbook/pediatric/

UCSF-specific resources:
ASP – focused questions M-F (day) 514-1275
Pediatric ID – detailed consult (24/7) 443-2384

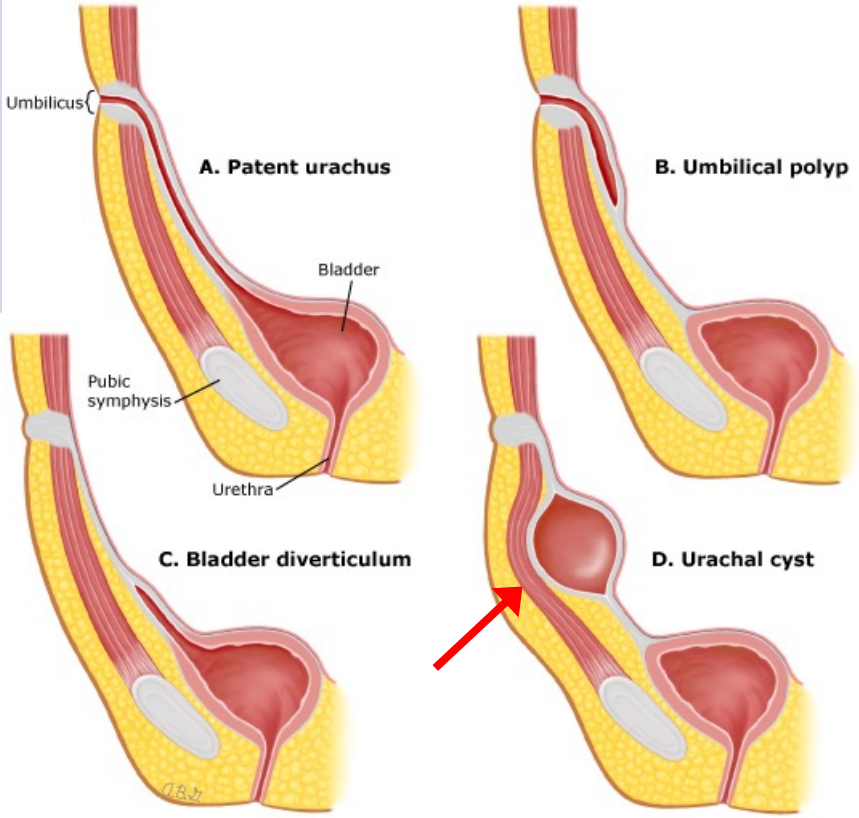
Online: idmp.ucsf.edu
- Dosing guidelines
- Empiric therapy guidelines
- Antibiotic susceptibility profiles

Choice of antibiotic for infected urachal cyst, outpatient and inpatient

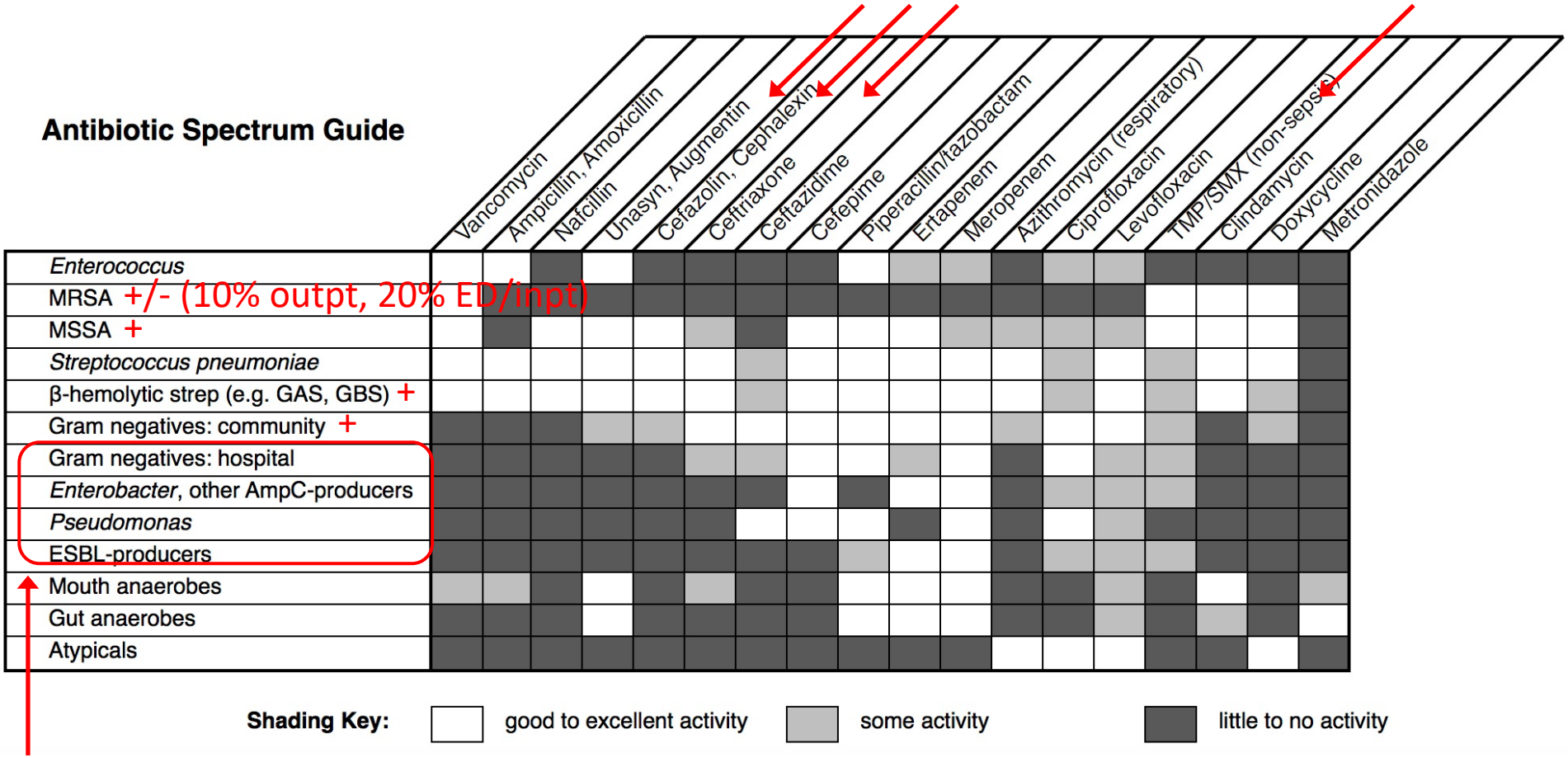
Key Questions	Example
1. What is going on with this patient? *The Clinical Syndrome* *--What is the location?* *--How does infection develop (where do the pathogens come from?)* *(e.g. contiguous, hematogenous, etc.)* *--Something anyone can get vs. special host susceptibility?*	Infected urachal cyst

My initial guess – seems like you could get infection coming from bladder with GI/GU flora (enteric Gram negative rods) OR coming from umbilicus with skin flora (Staph/Strep)

Up to Date supports this idea



Key Questions	Example
1. What is going on with this patient? *The Clinical Syndrome*	Infected urachal cyst
2. What organisms cause this clinical syndrome in this type of patient? *The Microbiologic Differential*	Gram negative enteric bacteria: *E. coli* *Klebsiella* *Proteus,* etc. Gram positive skin flora: *Staph aureus*, group A strep
3. What antibiotic(s) work against this organism in this condition? *Therapy Options*	Will look at spectrum guide next slide
4. What is the margin of error for initial choice of therapy? *--How sick is this patient?* *--What might happen if initial therapy is not active? (Bad outcome likely/unlikely)* *--Is there diagnostic uncertainty?*	Small or large urachal cyst? (possibility that it could rupture > peritonitis) Degree of systemic illness? Sepsis? Degree of localized inflammation? e.g. peritoneal signs? (possible impending rupture?)



Resistant GNR – depends on patient hospital/prior antibiotic exposure

Urgency spectrum?

Community acquired lobar pneumonia + effusion with influenza A detection

- 8 yo previously healthy boy presenting to ED (3rd visit)
  - 1st visit 6 days prior - diagnosed with influenza A
  - 2nd visit 4 days prior – diagnosed with superimposed lobar pneumonia – started azithromycin + oseltamivir
  - Now returns for worsened fevers, cough
- Exam:
  - Seems de-hydrated
  - Not toxic-appearing
- Labs:
  - WBC 17,000 (70% neutrophils)
  - ESR 68
  - CRP >32
  - Procalcitonin 2.5
- Chest X-ray:
  - Worse than prior
  - Possible effusion (same side as lobar infiltrate)

Procalcitonin (PCT):
Adult nl <0.25 ng/ml
Less pediatric data – OASIS study: CRP <4 mg/dL + PCT <1.75 ng/mL had an NPV of 0.90 (95% CI, 0.79-1.0) and specificity of 0.43 (95% CI, 0.30-0.55) for bacterial infection in children with SIRS admitted to PICU

Downes KJ, et al. JPIDS 2017

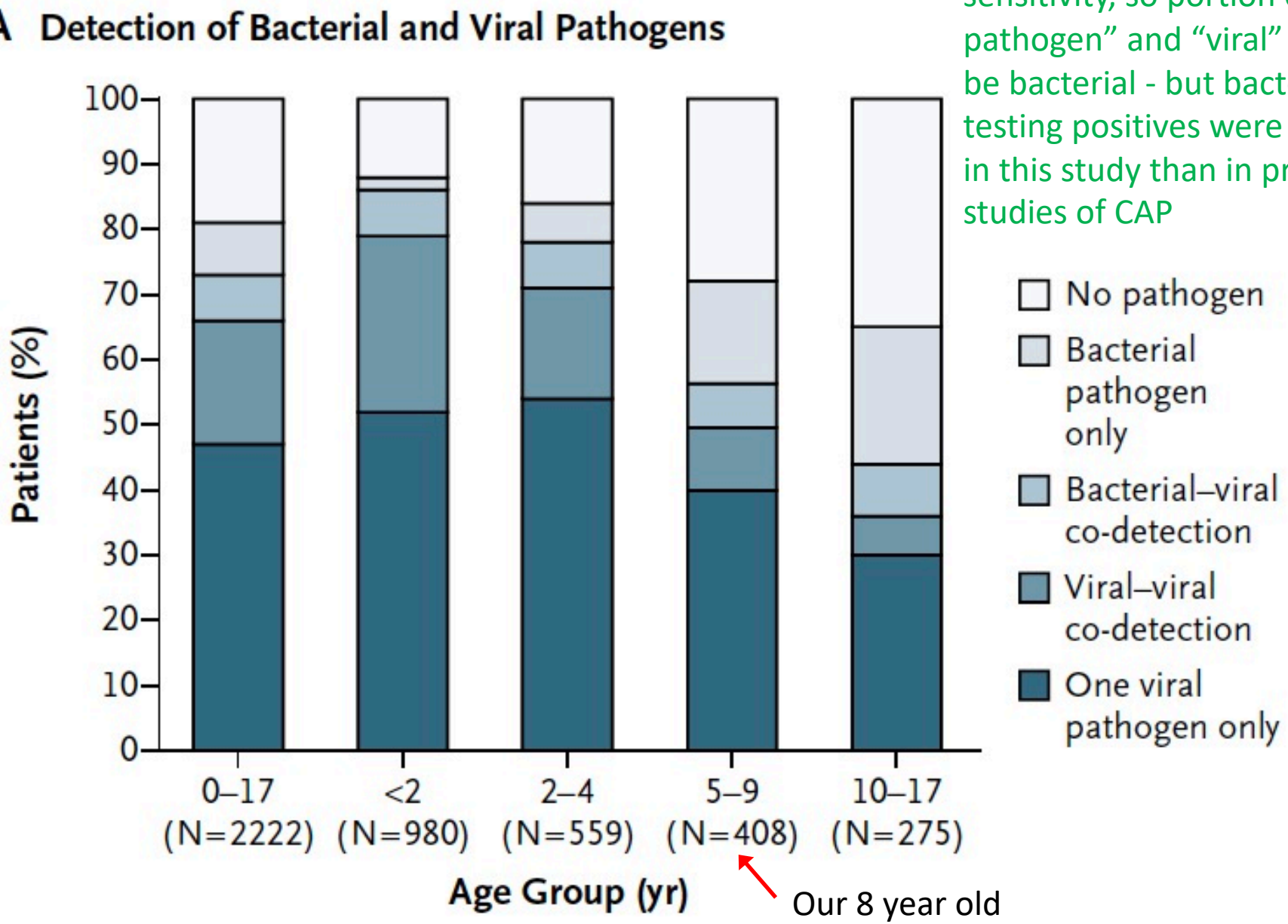
Key Questions	Example
1. What is going on with this patient? *The Clinical Syndrome*	Lobar pneumonia in context of influenza A infection + possible effusion (probably means trace or small, not moderate-large?) Did not improve with azithromycin x2d Elevated WBC + inflammatory markers
2. What pathogens cause this clinical syndrome? *The Microbiologic Differential*	???

Pediatric Community-Acquired Pneumonia Etiology of Pneumonia in the Community (EPIC) Study

- Etiology of Pneumonia in the Community (EPIC) study
  - Population-based cohort study of CAP in children (& adults) at 3 US sites, CDC-sponsored
  - Patients hospitalized at a study site without recent prior admission (excluded long term care residence, tracheostomy, transplant, oncology, advanced HIV, cystic fibrosis)
  - Expanded viral and bacterial testing (including molecular) of blood + respiratory samples
  - Strict pneumonia case definition with central radiographic review
- Of 2222 children with radiographically confirmed pneumonia + complete testing, a pathogen was detected in 1802 (81%):
  - Virus only (1 or more): 1472 (66%)
  - Bacteria only (1 or more): 175 (8%)
  - Both virus + bacteria: 155 (7%)

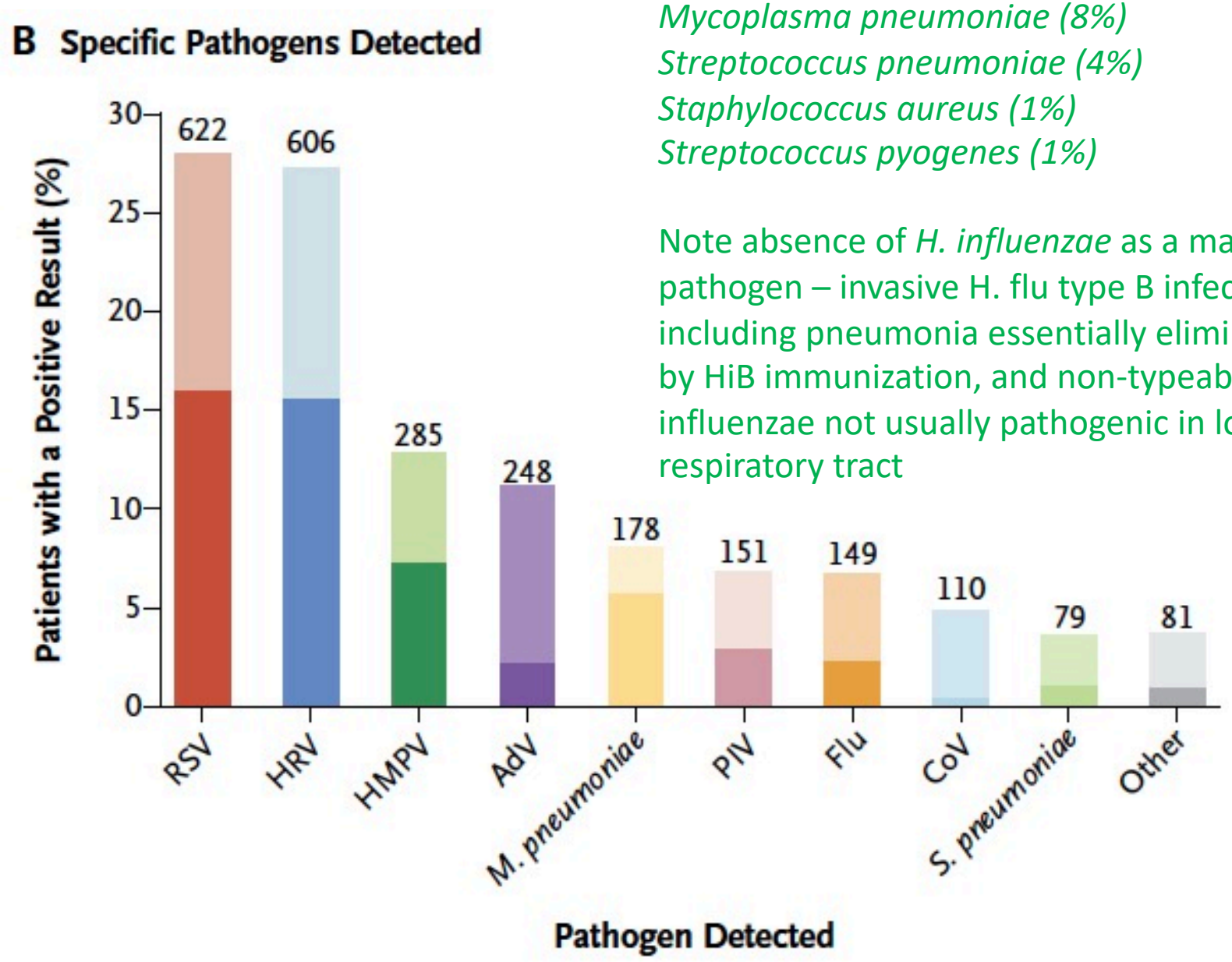
Jain S, et al. NEJM 2015

Bacterial testing has lower sensitivity, so portion of "no pathogen" and "viral" likely to be bacterial - but bacterial testing positives were lower in this study than in prior studies of CAP



Our 8 year old patient

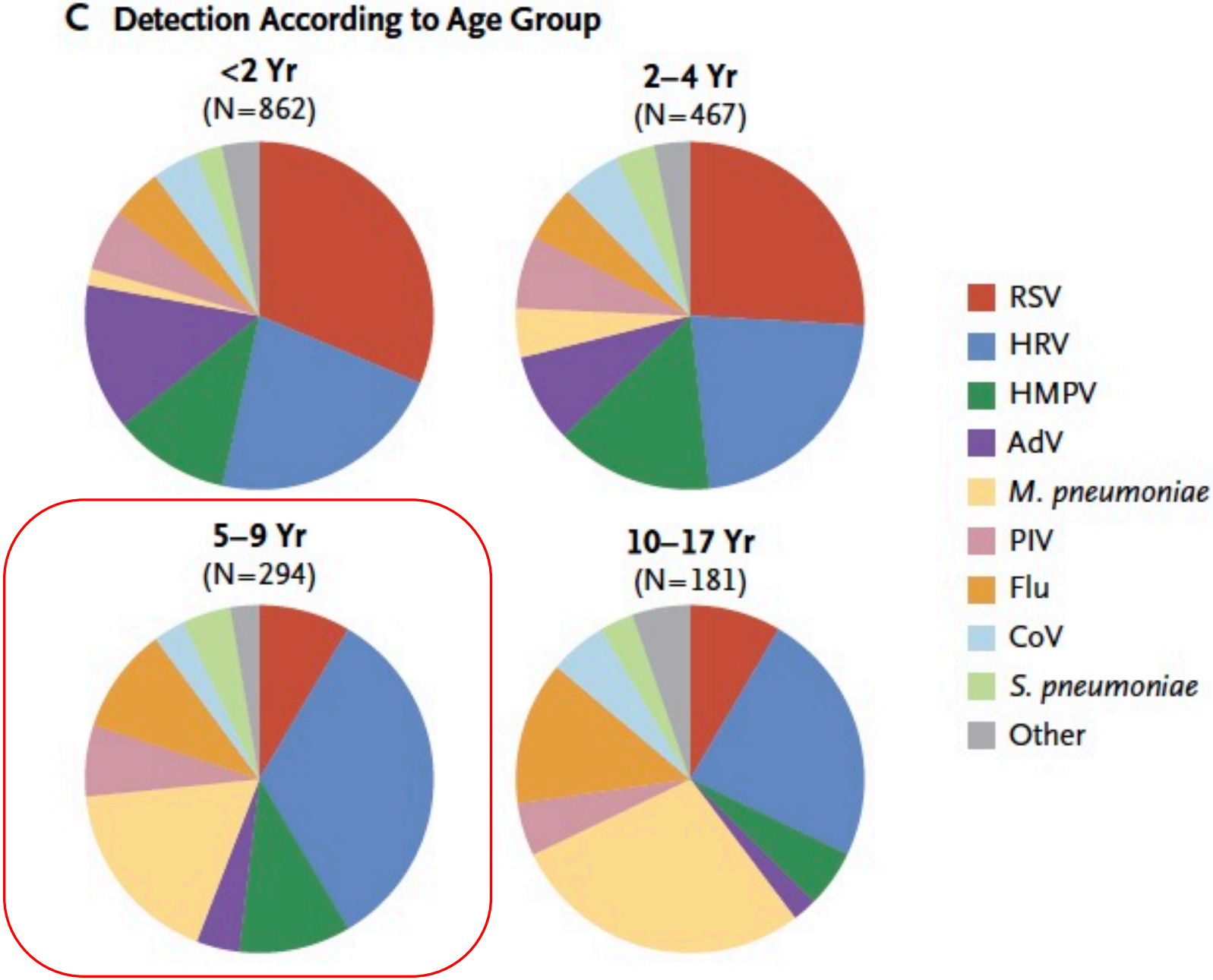
Jain S, et al. NEJM 2015



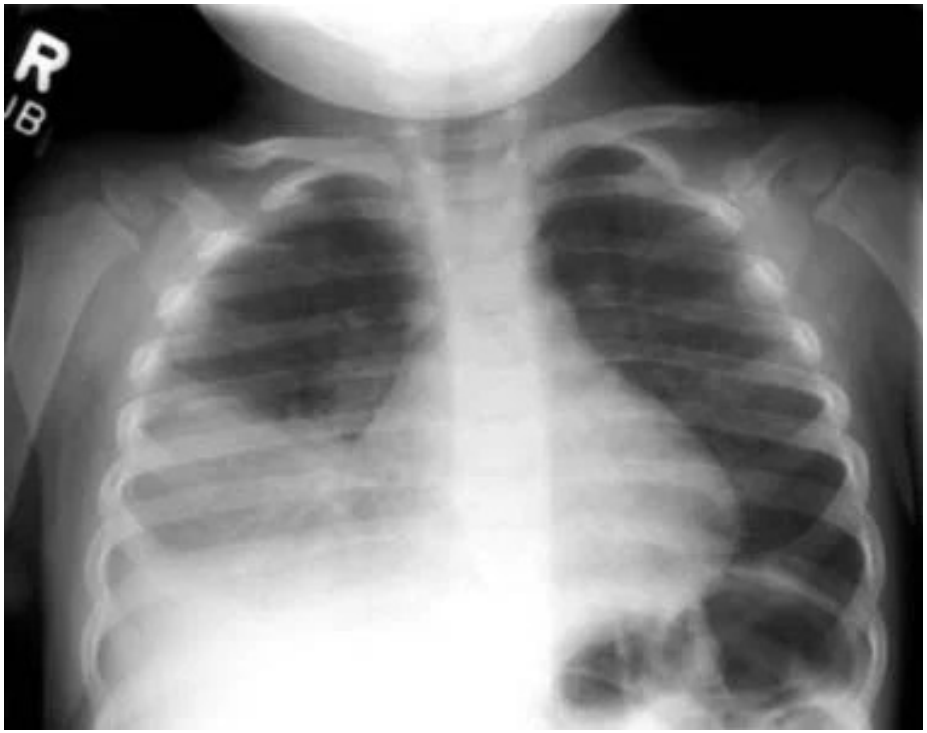
Most commonly identified bacteria:
Mycoplasma pneumoniae (8%)
Streptococcus pneumoniae (4%)
Staphylococcus aureus (1%)
Streptococcus pyogenes (1%)

Note absence of *H. influenzae* as a major pathogen – invasive H. flu type B infection including pneumonia essentially eliminated by HiB immunization, and non-typeable H. influenzae not usually pathogenic in lower respiratory tract

Jain S, et al. NEJM 2015


C Detection According to Age Group
<2 Yr
(N=862)
2–4 Yr
(N=467)
5–9 Yr
(N=294)
10–17 Yr
(N=181)
RSV
HRV
HMPV
AdV
M. pneumoniae
PIV
Flu
CoV
S. pneumoniae
Other

How should the radiographic finding of lobar pneumonia influence our microbiologic differential for CAP?

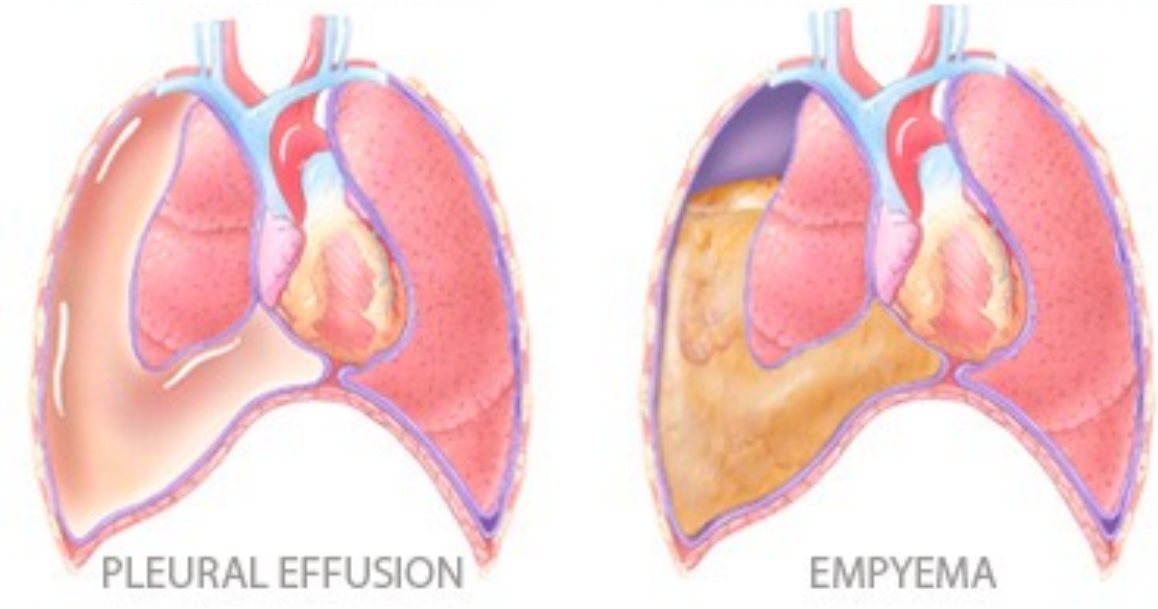


- Lobar pneumonia is considered highly specific for typical bacterial etiology but not highly sensitive (typical bacteria could also present with other patterns, e.g. bronchopneumonia)
- *S. pneumoniae* is most likely etiology
  - Urine pneumococcal antigen positive in 76% of children presenting to ED with lobar pneumonia (study from cusp of PCV7 era – could be different now)

Neuman MI, Harper MB. Pediatrics 2003

How should the radiographic finding of an effusion influence our microbiologic differential for CAP?

- Parapneumonic effusion = exudative pleural effusion associated with lung infection
  - Simple parapneumonic effusion – sterile, free-flowing, pleura is inflamed with leakage of fluid, protein, WBC due to adjacent pneumonia
    - Usually small, not causing significant respiratory impairment
  - Loculated parapneumonic effusion – septations due to progressive inflammation – may be sterile
  - Empyema – pleural fluid is grossly purulent or bacteria present – infection has spread from lung to adjacent pleural space
    - Usually moderate to large size, compressing lung +/- mediastinal shift



Effusion size:

- Small: <10mm or < ¼ hemithorax opacified
- Moderate:
  - ¼ to ½ hemithorax opacified
- Large:
  - >½ hemithorax opacified

Bradley JS, et al. CID 2011

How should the radiographic finding of an effusion influence our microbiologic differential for CAP?

- Etiologies:
  - Small>moderate>large, simple>loculated>empyema:
    - *Streptococcus pneumoniae* ~ 70-80%
    - *Staphylococcus aureus* (MSSA, MRSA) ~ 10%
    - Group A streptococcus (beta-hemolytic) ~ 10%
    - Viridans group streptocci ~ 1%
    - *H. influenzae* type B in pre-HiB vaccine era (now nearly eliminated)
  - Small, simple effusions (without progression to empyema)
    - *Mycoplasma pneumoniae*
    - Viral pneumonia

- Does the presence of an effusion define “complicated pneumonia?
  - IDSA guidelines: parapneumonic effusions, multilobar disease, abscesses or cavities, necrotizing pneumonia, empyema, pneumothorax or bronchopleural fistula; or pneumonia that is a complication of bacteremic disease that includes other sites of infection
  - Other sources have suggested that small simple effusion should be considered “uncomplicated”

Blaschke A, et al. PIDJ 2011; Perez VP, et al. Diagn Microbiol Infect Dis 2016; Bradley JS, et al. CID 2011; Jain S, et al. AAP Section on Emergency Medicine 2017

How should preceding/concurrent influenza influence our microbiologic differential for CAP?

Table 4. Bacterial Pathogens Identified From Positive Bacterial Cultures Among Children Hospitalized With Influenza-Associated Respiratory Complications or Bacteremia/Sepsis, Emerging Infections Program Surveillance Sites, 2003–2010

Pathogen	Pneumonia, No. (%) (n = 49)		Lung Abscess/ Empyema, No. (%) (n = 12)		Bacteremia/Sepsis, No. (%) (n = 43)	
Streptococcus pneumoniae						
Overall	23	(47)	7	(58)	19	(44)
Serotype 19A	7	(30)	2	(29)	6	(32)
Serotype 7F	6	(26)	2	(29)	4	(21)
Other serotype[a]	4	(17)	1	(14)	5	(26)
Serotyping results unavailable	6	(26)	2	(29)	4	(21)
Staphylococcus aureus						
Overall	17	(35)	4	(33)	14	(33)
Methicillin susceptible	9	(53)	1	(25)	8	(57)
Methicillin resistant	5	(29)	3	(75)	3	(21)
Methicillin susceptibility testing results unavailable	3	(18)	0	(0)	3	(21)
Streptococcus pyogenes						
Overall	2	(4)	1	(8)	2	(5)
Other	7	(14)	0	(0)	8	(19)

Meta-analysis of co-infection studies:

- 35% (95%CI 14-56%) *S. pneumoniae*
- 28% (95% CI 16-40%) *S. aureus*

Analysis based on positive cultures, not molecular testing – *S. pneumoniae* probably underrepresented?

Dawood FT, et al. JID 2014,
Klein EY, et al. Influenza Other Respir Viruses 2016

How should non-response to azithromycin influence our microbiologic differential for CAP?

Invasive pneumococcal isolate susceptibilities from CDC Active Bacterial Core Surveillance, 2016

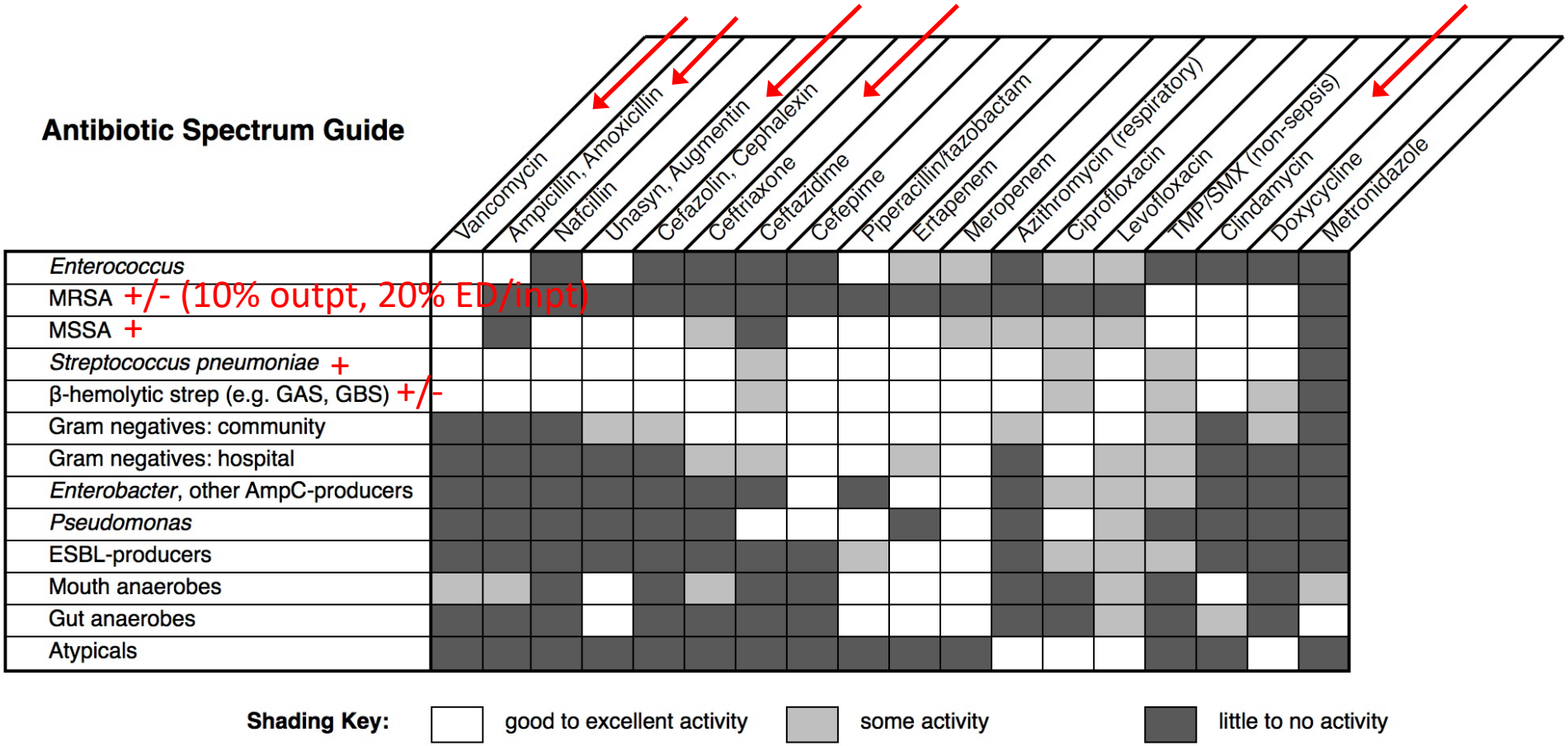
(infer azithromycin from erythromycin)

Antibiotic	S*	I†	R‡
Susceptibility			
Penicillin+	96.0	1.8	2.2
Cefotaxime	97.5	2.0	0.4
Erythromycin	69.3	0.0	30.7
TMP/Sulfa	81.7	12.3	6.0
Tetracycline	87.8	0.0	12.2
Levofloxacin	99.8	0.0	0.2
Vancomycin	100	0.0	0.0

Staphylococcus aureus – from Kaier NCAL antibiogram (2017):
--73% MSSA susceptible to azithromycin
--17% MRSA susceptibile to azithromycin

Key Questions	Example
1. What is going on with this patient? *The Clinical Syndrome*	Lobar pneumonia in context of influenza A infection + possible effusion (probably means trace or small, not moderate-large?) Did not improve with azithromycin x2d Elevated WBC + inflammatory markers
2. What pathogens cause this clinical syndrome? *The Microbiologic Differential*	Radiographic appearance + inflammatory markers increase suspicion for bacterial superinfection Lobar pneumonia most likely *S. pneumoniae* Preceding influenza increases likelihood of *Staphylococcus aureus* Preceding azithromycin doesn't modify differential (neither organism highly susceptible to it) Our guess: ~ 75% *S. pneumoniae* ~ 20% *S. aureus* (primarily b/c of flu) ~ 5% other e.g. group A strep

Antibiotic Spectrum Guide



Urgency spectrum?

--How sick is this patient?
--What might happen if initial therapy is not active? (Bad outcome likely/unlikely)

When should a macrolide be used in CAP?

Site of care	Empiric therapy: Presumed bacterial pneumonia	Empiric therapy: Presumed atypical pneumonia
Outpatient		
<5 years old (preschool)	Amoxicillin, oral (90 mg/kg/day in 2 doses[b]) Alternative: oral amoxicillin clavulanate (amoxicillin component, 90 mg/kg/day in 2 doses[b])	Azithromycin oral (10 mg/kg on day 1, followed by 5 mg/kg/day once daily on days 2–5); Alternatives: oral clarithromycin (15 mg/kg/day in 2 doses for 7-14 days) or oral erythromycin (40 mg/kg/day in 4 doses)
≥5 years old	Oral amoxicillin (90 mg/kg/day in 2 doses[b] to a maximum of 4 g/day[c]); for children with presumed bacterial CAP who do not have clinical, laboratory, or radiographic evidence that distinguishes bacterial CAP from atypical CAP, a macrolide can be added to a β-lactam antibiotic for empiric therapy; alternative: oral amoxicillin clavulanate (amoxicillin component, 90 mg/kg/day in 2 doses[b] to a maximum dose of 4000 mg/day, eg, one 2000-mg tablet twice daily[b])	Oral azithromycin (10 mg/kg on day 1, followed by 5 mg/kg/day once daily on days 2–5 to a maximum of 500 mg on day 1, followed by 250 mg on days 2–5); alternatives: oral clarithromycin (15 mg/kg/day in 2 doses to a maximum of 1 g/day); erythromycin, doxycycline for children >7 years old
Inpatient (all ages)[d]		
Fully immunized with conjugate vaccines for *Haemophilus influenzae* type b and *Streptococcus pneumoniae*; local penicillin resistance in invasive strains of pneumococcus is minimal	Ampicillin or penicillin G; alternatives: ceftriaxone or cefotaxime; addition of vancomycin or clindamycin for suspected CA-MRSA	Azithromycin (in addition to β-lactam, if diagnosis of atypical pneumonia is in doubt); alternatives: clarithromycin or erythromycin; doxycycline for children >7 years old; levofloxacin for children who have reached growth maturity, or who cannot tolerate macrolides

AAP guideline:

"predominantly school-aged children and adolescents"

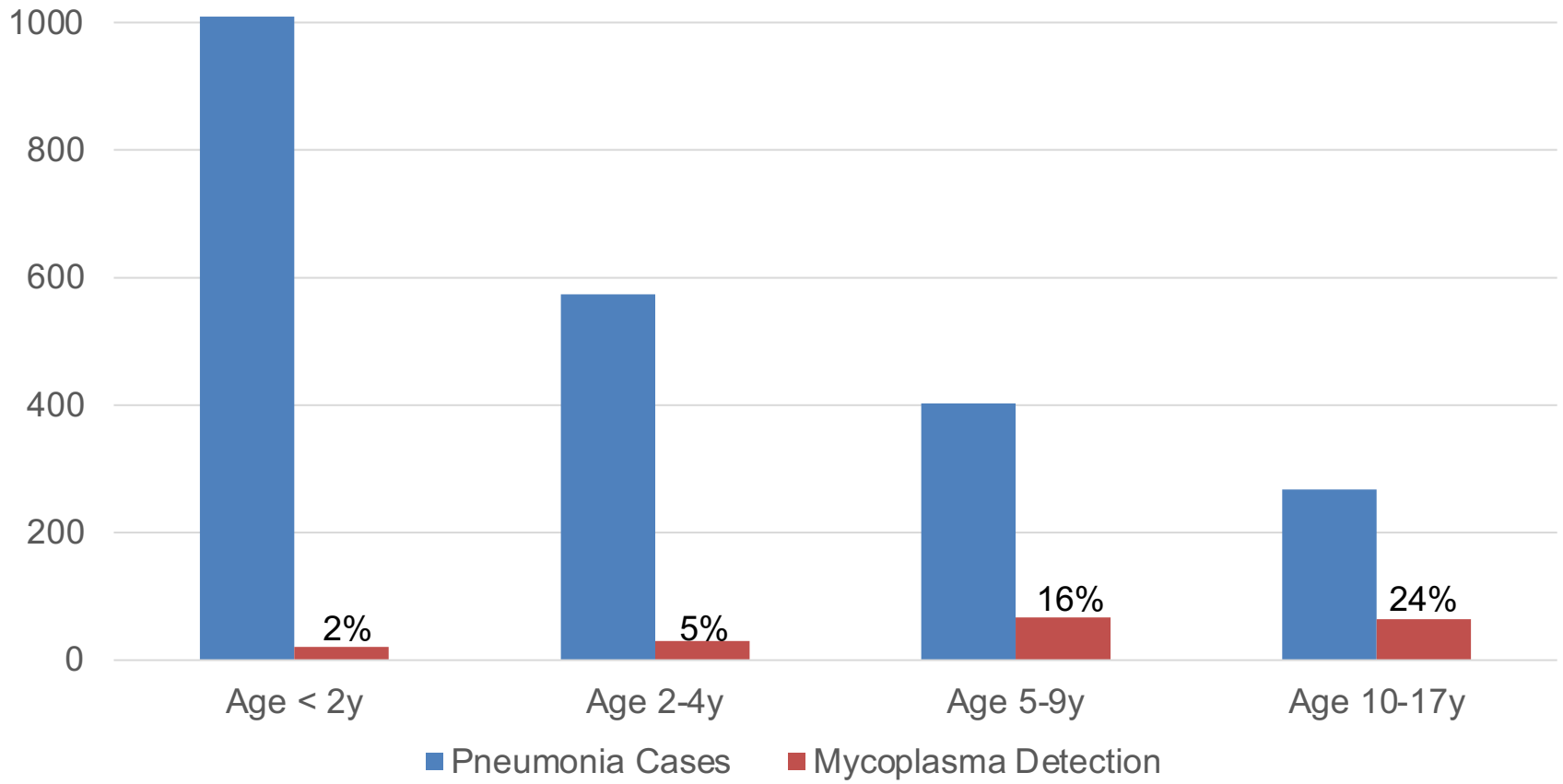
"Atypical pneumonia caused by *Mycoplasma* is characteristically slowly progressing, with malaise, sore throat, low-grade fever, and cough developing over 3-5 days."

Note: macrolide therapy recommendations in guideline are "weak recommendation, moderate quality evidence"

No RCTs supporting macrolide efficacy

Bradley JS, et al. CID 2011

Mycoplasma pneumoniae in EPIC Study



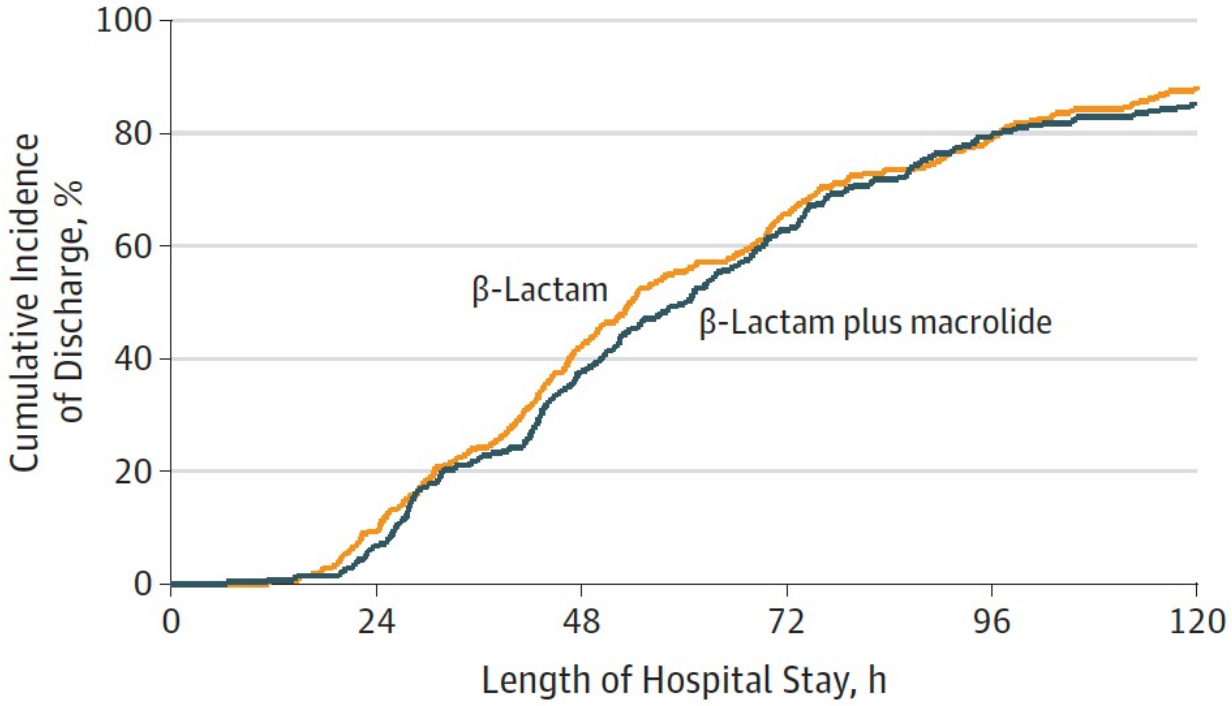
- Age group was strongest predictor associated with Mycoplasma+ cases
- No specific clinical or radiographic findings identified distinguishing Mycoplasma+ cases from Mycoplasma- cases
- Limitations: Mycoplasma co-detection with other pathogens was common (25% of Mycoplasma+ cases), Mycoplasma detection may not = disease

Kutty PK, et al. CID 2018

Beta lactam + macrolide vs. beta lactam alone for pediatric inpatient pneumonia treatment

EPIC study cohort

Figure 2. Cumulative Incidence of Discharge According to Antibiotic Treatment and Propensity Score–Matched Cohort



No. at risk						
β-Lactam	280	254	162	96	59	33
β-Lactam plus macrolide	280	261	174	104	57	41

Cumulative incidence of discharge according to antibiotic treatment in a cohort of children matched 1:1 according to their propensity to receive β-lactam plus macrolide combination therapy, conditional on baseline demographic, clinical, and radiographic characteristics.

Williams DJ, et al. JAMA Pediatrics 2018

Table 3. Adjusted Hazard Ratios for Time to Discharge

Subgroup	Patients, No.	Adjusted Hazard Ratio (95% CI)[a]
Age ≥5 y	373	1.08 (0.86-1.36)
Atypical bacteria detected	110	1.07 (0.59-1.96)
Admitted to intensive care	187	0.86 (0.54-1.36)
Acute wheezing	576	0.93 (0.74-1.16)
Hospital A[b]	514	0.90 (0.72-1.13)
Hospital B[b]	416	1.05 (0.82-1.36)
Hospital C[b]	403	0.84 (0.61-1.16)

[a] The hazard ratio compares the rate (hazard) of discharge between children receiving β-lactam plus macrolide combination therapy and those receiving β-lactam monotherapy. A hazard ratio less than 1.0 indicates a slower rate of discharge for children receiving combination therapy compared with monotherapy. Covariates included in the unmatched, multivariable models and the propensity score–matched models were identical.

[b] The names of hospitals have intentionally been kept anonymous in this table.

Williams DJ, et al. JAMA Pediatrics 2018

- *Non-perforated appendicitis. Gave kid Cefoxitin, got hives and itchy throat 3 min later. Had to switch my antibiotics and was wondering what the best choices would be. i.e. when they have a true allergy to a cephalosporin. I ended up using Cipro and Flagyl after discussing with surgery, other option was Ertapenem as a sole agent. Could we go over the latest recommendation of which abx to pick for intra abdominal infections when PCN a/o Ceph allergic? Also when to use Cipro esp given the association with tendinopathies.*

- *Febrile infant (<28 days age) found to have E. Coli UTI - both of these situations have come up - unsuccessful LP so no CSF culture and CSF with pleocytosis in setting of traumatic tap but negative CSF culture, both with negative blood cultures, the question of need to treat for meningitis or not? Also, choice of PO antibiotics amoxicillin vs keflex.*

TABLE 1. Characteristics of Infants With First Episode of SBI

Variable	Bacteremia N = 129 (%)	UTI N = 778 (%)	Meningitis N=16 (%)
Male	74/129 (57)	462/778 (59)	7/16 (44)
Febrile	115/122 (94)	575/676 (85)	14/15 (93)
Ill-appearing	21/123 (17)	46/670 (7)	10/16 (63)
White blood cell count ≥15,000 × 10^9/L	57 /129 (44)	300/672 (45)	5/16 (31)
Viral co-infection	2 /34 (6)	11/119 (9)	0/6 (0)
Abnormal urinalysis	66/114 (58)	615/671 (92)	6/15 (40)
Abnormal chest radiograph	14/82 (17)	39/349 (11)	2 /13 (15)

TABLE 2. Culture Acquisition by Age in Infants With SBI

Cultures Obtained	Age (Days) 7–28	29–60	61–90	Total
Complete evaluation (blood, urine and CSF cultures)	147	137	33	317
Blood and urine cultures only	84	173	153	410
Blood and CSF only	1	1	0	2
Urine and CSF only	1	1	1	3
Blood culture only	1	2	3	6
Urine culture only	5	30	69	104
Total	239	344	259	842

Observational study from Kaiser Northern California

"Incomplete evaluation" is more typical than "complete evaluation" except in the youngest infants

Greenhow TL, et al. PIDJ 2014

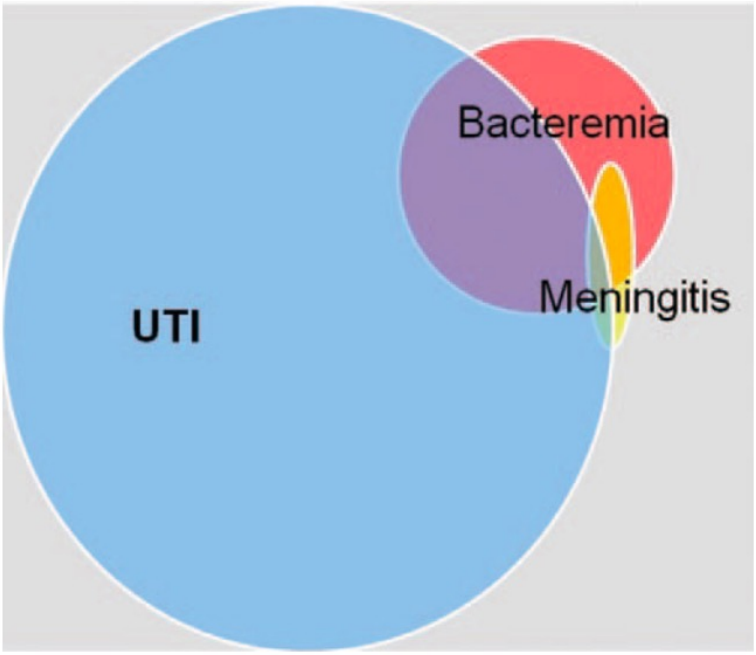


FIGURE 1. Venn diagram illustrating the distribution of infections with 1 source and >1 source.

TABLE 4. Pathogen Source: First Episode of SBI

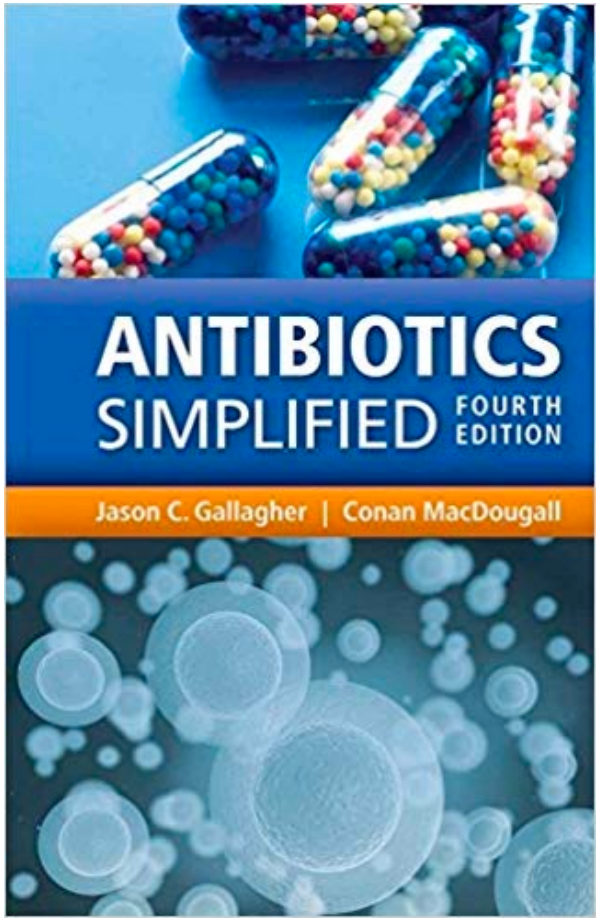
	Age (Days)			
Source of Pathogen	7–28	29–60	61–90	Total
Blood only	22	22	9	53
Urine only	184	294	231	709
CSF only	0	1	1	2
Blood/urine	27	21	16	64
Blood/CSF	5	2	2	9
CSF/urine	1	1	0	2
Blood/urine/CSF	0	3	0	3
Total (>1 source)	239 (33)	344 (27)	259 (18)	842 (78)

Meningitis accompanying UTI without bacteremia is possible but extremely rare in this cohort:

2/842 (0.2%) overall
1/239 (0.4%) in age 7-28 days

Greenhow TL, et al. PIDJ 2014

Favorite Resources



Really good book to learn antibiotics + spectrum, & basic clinical microbiology

Dosing: Lexi-Comp

Adjustment for renal failure & dialysis:
https://kdpnet.kdp.louisville.edu/drugbook/pediatric/

UCSF-specific resources:
ASP – focused questions M-F (day) 514-1275
Pediatric ID – detailed consult (24/7) 443-2384

Online: idmp.ucsf.edu
- Dosing guidelines
- Empiric therapy guidelines
- Antibiotic susceptibility profiles