Pregnancy and lactation with antibiotics: Where's the data?

YoungYoon Ham, PharmD BCIDP
Oregon Health & Science University
Pharmacy Services – ID division
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Some stats

- Antibiotics – 80% of all prescriptions during pregnancy
  - 20-25% of women receive an abx during pregnancy
- Most common infections treated during pregnancy
  - Urinary Tract Infection (UTI)
  - Sexually Transmitted Infections (STI)
  - Upper Respiratory Tract Infection (URTI)
- Untreated infections associated with fetal risk
  - Spontaneous abortion, prematurity, low birth weight

Where’s the data?

- Exclusion from studies

- Only 10% medications marketed since 1980 have sufficient pregnancy data

What are we concerned about?

- Short term
  - Birth defects
  - Spontaneous abortion
  - Low birth weight
- Long term
  - Childhood obesity
  - Cerebral palsy, epilepsy, asthma

The old (simple or simplistic) system

- FDA pregnancy risk categories
  - A – No risk in human studies. Adequate and well controlled human studies have failed to demonstrate a risk to the fetus.
    - NO ABX FIT INTO THIS CATEGORY
  - B – No risk in animal studies.
  - C – Animal studies show adverse reaction.
  - D – Positive evidence of risk in humans
  - X – Contraindicated in pregnancy

The new system

- FDA narrative sections
  - Pregnancy
    - Include labor and delivery
  - Lactation
    - Includes nursing mothers
  - Female and male reproductive potential

Other things to keep in mind

- Pharmacokinetic changes
  - Increase in total body water and blood volume (40%-50%)
    - Increased volume of distribution
  - Increase in creatinine clearance
  - Alterations in GI motility
    - Delayed onset of action
  - Decrease in albumin and pH changes leading to ↓ ↓ protein binding??

Bookstaver et al. Pharmacotherapy 2015

Green light

- Hello penicillins (my old friends)
  - Including beta lactamase inhibitors
- Cephalosporins
  - Ceftriaxone – Kernicterus
- Ertapenem/Meropenem

Bookstaver et al. Pharmacotherapy 2015

Green light

- Azithromycin
  - No harm in animal studies
- Vancomycin
- Clindamycin (Not vaginal route)
  - Study of over 600 newborns with first trimester exposure found no defects
  - No evidence for late in pregnancy for oral, evidence of harm for vaginal route
- Fosfomycin

Bookstaver et al. Pharmacotherapy 2015

Yellow light

- Imipenem-cilastatin
  - PK changes
- Erythromycin
  - Association with cardiac defects and pyloric stenosis?
  - Later studies found no such association
- Clarithromycin
  - Rat studies – cardiac abnormalities
  - Cleft palate in murine studies and retarded fetal growth in monkeys

Bookstaver et al. Pharmacotherapy 2015

Yellow light

- Daptomycin
  - Isolated reports seem safe in humans
  - No evidence of harm from animal studies
- Nitrofurantoin
  - Risk in 3rd trimester, hemolytic anemia in newborns
  - Associated with birth defects in first trimester

Bookstaver et al. Pharmacotherapy 2015

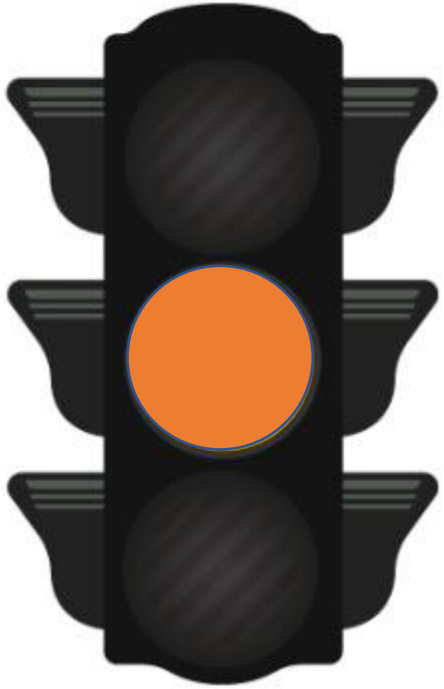
Yellow light

- Linezolid/Tedizolid
  - Mild fetal toxicities in rats and rabbits, decreased body weight and increase in cartilage abnormalities
  - Mixed with other animal data which saw no defects
- Metronidazole
  - Contraindicated in first trimester – preterm birth

Bookstaver et al. Pharmacotherapy 2015

Orange light?

- Sulfamethoxazole/trimethoprim
  - Ok in 2nd trimester?
  - 1st trimester – folate antagonist
  - 3rd trimester -- Kernicterus
- Aminoglycosides
  - Gentamicin/Amikacin
  - Cross placenta
  - May cause toxicities, especially in first trimester of pregnancy
- Oritavancin/Dalbavancin
  - Evidence of fetal harm in animal studies



Bookstaver et al. Pharmacotherapy 2015

Red light

- Fluoroquinolones
  - Fetal harm in animal studies
- Tetracyclines
  - Proven teratogens
  - Discoloration of bones and teeth
  - Tick-borne illness?
- Streptomycin
  - Documented bilateral congenital deafness
- Tigecycline

Bookstaver et al. Pharmacotherapy 2015

Lactation

- Generally, most things are fine
- Concerns include hypersensitivity reactions, diarrhea, thrush, and disruption of gastrointestinal flora.
- And man, if you thought pregnancy + abx was lacking in data…

Lactation medication ratings

- L1 – Safest
- L2 – Safer
- L3 – Probably safe
- L4 – Possibly hazardous
- L5 – Hazardous

How to gauge infant exposure?

- Infant dose
  - **Estimated daily infant dose via breast milk (mg/kg/day) = drug concentration in breast milk (mg/mL) x volume breast milk ingested (mL/kg/day)**
- Relative infant dose (RID)
  - **Estimated daily infant dose via breast milk (mg/kg)*100/Mother's daily dosage (mg/kg)**

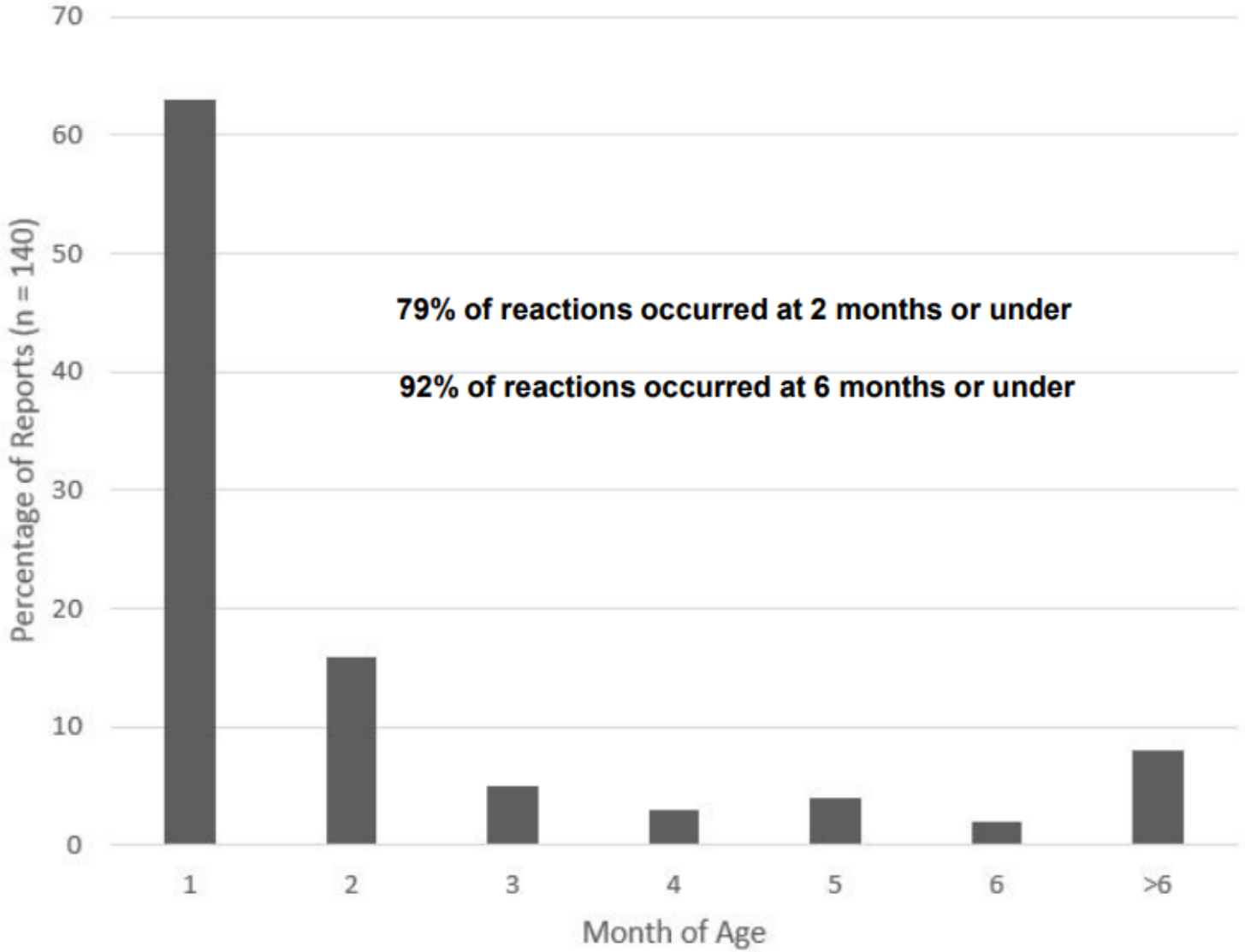
Anderson PO et al. Clin Pediatr 2016;55:236-44

RID classification system

- Acceptable – < 10% of maternal dosage
  - 87% of all medications fall into this category
- Caution – 10% to 25% of maternal dosage
- Unacceptable – >25% of maternal dosage
  - inherent toxicity (eg, cytotoxics)
  - credible reported toxicity

Anderson PO et al. Clin Pediatr 2016;55:236-44

Adverse Reactions by Age



Anderson PO et al. Clin Pediatr 2016;55:236-44

Potentially avoid

- Doxycycline or minocycline – dental staining, decreased bone growth
  - However, probably bound by calcium in breastmilk, and doxycycline can be used in children <8 years for up to 21 days.
- Fluoroquinolones – not well studied, though thought to get bound by calcium in breastmilk

Antibacterial Medication Use During Pregnancy and Risk of Birth Defects

- Population based, multisite, case-control study of women who had pregnancies affected by 1 of more than 30 major birth defects.
- Case N= 13,155, Control N= 4941
- Main exposure – Reported maternal use of antibacterials
- Main outcome measure – Odds ratios of association between antibacterial use and selected birth defects

Crider et al. Arch Pediatr Adolesc Med. 2009.

Antibacterial Medication Use During Pregnancy and Risk of Birth Defects

- Sulfonamides
  - Anencephaly (adjusted OR [AOR]=3.4; 95% confidence interval [CI], 1.3-8.8)
  - Hypoplastic left heart syndrome (AOR=3.2; 95% CI, 1.3-7.6)
  - Coarctation of the aorta (AOR=2.7; 95% CI, 1.3-5.6)

- Nitrofurantoin
  - Anophthalmia or microphthalmos (AOR=3.7; 95% CI, 1.1-12.2)
  - Atrial septal defects (AOR=1.9; 95% CI, 1.1-3.4)
  - Cleft lip with cleft palate (AOR=2.1; 95% CI, 1.2-3.9)

Crider et al. Arch Pediatr Adolesc Med. 2009.

Criticisms of the Crider study

- Recall bias
- No confirmation of antibiotic
- 35% of women could not recall the name of the antibiotic they were given

Asymptomatic Bacteriuria/UTI

- First trimester
  - Penicillins/cephalosporins
  - Fosfomycin?
- Second trimester
  - Nitrofurantoin
  - Penicillins/cephalosporins
  - Sulfamethoxazole/trimethoprim
- Third trimester
  - Nitrofurantoin (not in the last few weeks)
  - Penicillins/cephalosporins

Syphilis

- Penicillin/Penicillin/Penicillin!!!
- Desensitize if you must
- Prevention of congenital syphilis not guaranteed even if mother is treated successfully

Alternate treatment studies

- Ceftriaxone 250 mg daily for variable courses (7-10 days for one or two courses)
  - No congenital syphilis, mom cured
- Erythromycin
  - Congenital syphilis at birth, mom cured
- Azithromycin
  - Congenital syphilis at birth, mom cured
- Tetracycline
  - Congenital syphilis at birth, mom failed treatment

Roberts CP, et al. *Sex Transm Dis*. 2019.

A note about penicillin allergies

- Most commonly reported medication allergy
- Less than 10% of patients who report an allergy are truly allergic
- Approximately 50% of penicillin allergies fade after 5 years and greater than 80% after 10 years
- Discrepancies are multifactorial and may include mislabeling of adverse events and misreported patient history in addition to waning sensitivities

Shenoy E, et al. JAMA. doi:10.1001/jama.2018.19283

Cephalosporin allergies

- Cephalosporin allergies are not a class effect
- Detailed interview can be helpful in narrowing down cephalosporin allergies

Fig. 1 **General structure of cephalosporins**

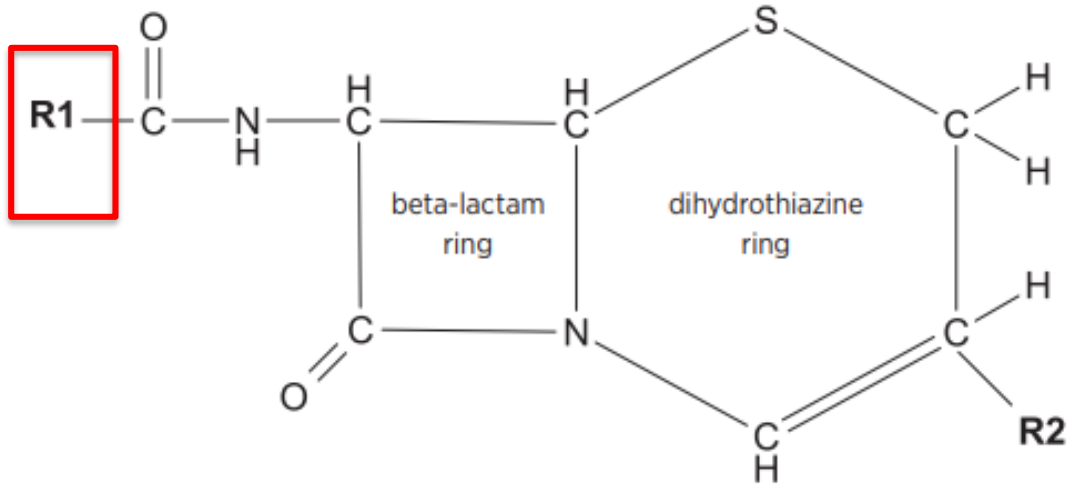
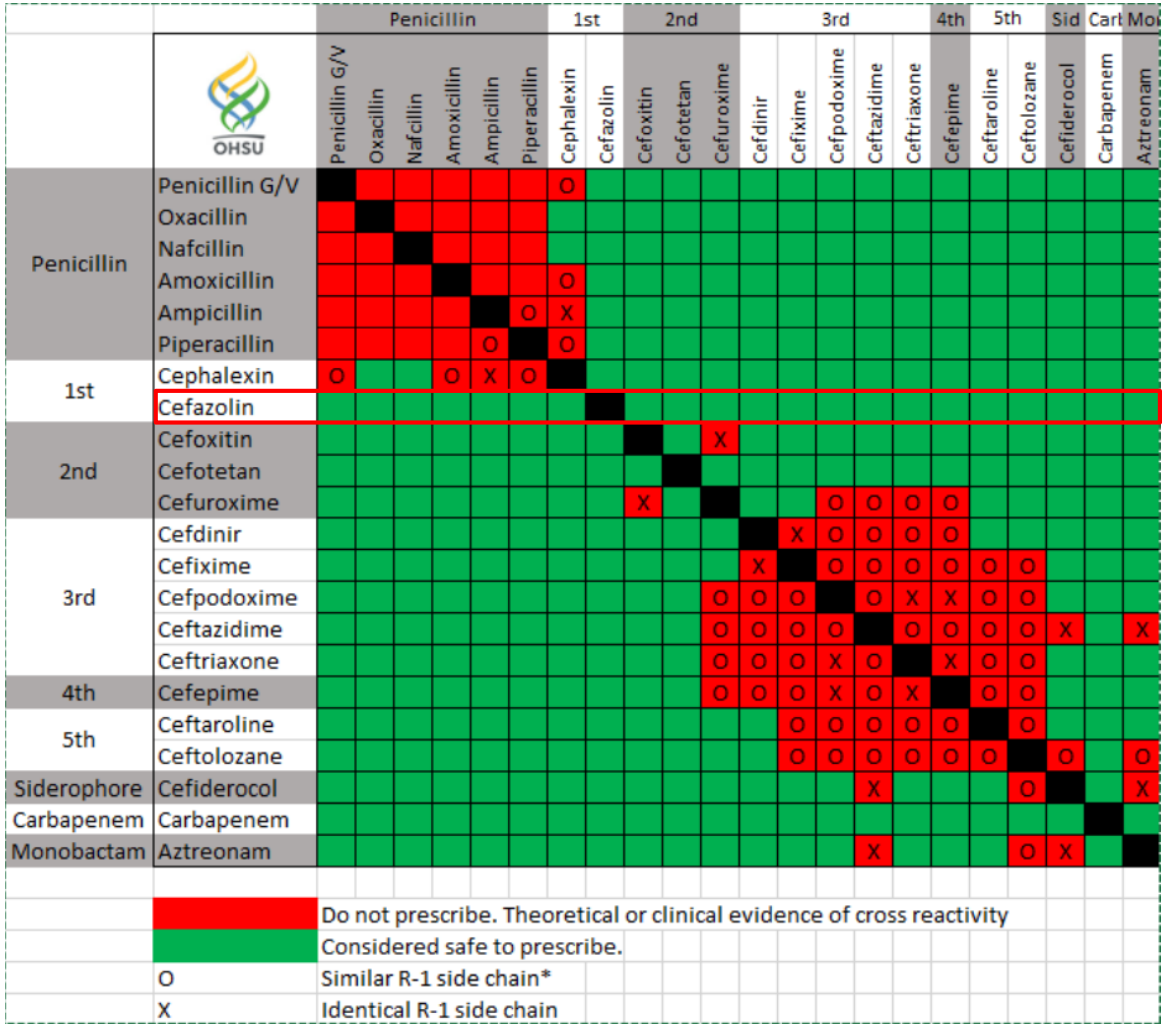


Image source: Yuson et al. Australian Prescriber Vol 41, N 2. April 2018

Cross reactivity

- Early studies were confounded by contamination
- Dependent on the R1 side chain



		Penicillin						1st		2nd			3rd					4th	5th		Sid	Carb	Mon
	OHSU	Penicillin G/V	Oxacillin	Nafcillin	Amoxicillin	Ampicillin	Piperacillin	Cephalexin	Cefazolin	Cefoxitin	Cefotetan	Cefuroxime	Cefdinir	Cefixime	Cefpodoxime	Ceftazidime	Ceftriaxone	Cefepime	Ceftaroline	Ceftolozane	Cefiderocol	Carbapenem	Aztreonam
Penicillin	Penicillin G/V	■						O															
	Oxacillin		■																				
	Nafcillin			■																			
	Amoxicillin				■			O															
	Ampicillin					■	O	X															
	Piperacillin					O	■	O															
1st	Cephalexin	O			O	X	O	■															
	Cefazolin								■														
2nd	Cefoxitin									■		X											
	Cefotetan										■												
	Cefuroxime									X		■			O	O	O	O					
3rd	Cefdinir												■	X	O	O	O	O					
	Cefixime												X	■	O	O	O	O	O	O			
	Cefpodoxime											O	O	O	■	O	X	X	O	O			
	Ceftazidime											O	O	O	O	■	O	O	O	O	X		X
	Ceftriaxone											O	O	O	X	O	■	X	O	O			
4th	Cefepime											O	O	O	X	O	X	■	O	O			
5th	Ceftaroline													O	O	O	O	O	■	O			
	Ceftolozane													O	O	O	O	O	O	■	O		O
Siderophore	Cefiderocol															X				O	■		X
Carbapenem	Carbapenem																					■	
Monobactam	Aztreonam															X				O	X		■

	Do not prescribe. Theoretical or clinical evidence of cross reactivity
	Considered safe to prescribe.
O	Similar R-1 side chain*
X	Identical R-1 side chain

Resources

- Lexicomp – Briggs section or Lexi section on pregnancy
- LactMed: https://www.ncbi.nlm.nih.gov/books/NBK501922/
- Drugs in Pregnancy and Lactation: A reference guide to fetal and neonatal risk – Gerald Briggs

Summary

- Penicillins/cephalosporins if at all possible in this population
- Allergies should be evaluated
- Lactation is probably fine regardless
- Lexicomp/Briggs are reliable resources