IS RESISTANCE FUTILE? ANTIMICROBIAL RESISTANCE IN PEDIATRICS

Amanda Goddard, MD
Pediatric Infectious Diseases
OBJECTIVES

1. Brief overview antibiotic development and resistance
2. Review gram negative cephalosporin resistant community acquired urinary tract infections
3. Discuss potentially avoidable and unavoidable selective pressures for bacterial antibiotic resistance
2 YEAR OLD FEMALE WITH 3 DAYS OF FEVER, DECREASED APPETITE AND ACTIVITY

Toilet training, has regressed with urination
On exam possible lower abdominal tenderness

URINE DIP STICK TESTING POSITIVE FOR LEUKOCYTE ESTERASE AND NITRITE

Cephalexin prescribed
Urine culture sent

LAB CALLS URINE CULTURE WITH ESBL ESCHERICHIA COLI

Plan to check lab report when break from clinic
Not your primary patient so wonder if risk factors

You have treated numerous MRSA skin infections but not extended spectrum beta-lactamase (ESBL) producing Enterobacterales (aka Enterobacteriaceae) UTIs, is this common in healthy outpatient children?
I’m confused about what to call enteric Gram-negative bacilli. It’s so simple!

We used to refer to these as the family Enterobacteriaceae, but now they make up seven different families. We should talk about the order instead.

The order ‘Enterobacteriales’ was suggested, but it was not validly published and did not follow the rules of nomenclature. The accepted name for the order is Enterobacterales, with no i.

Yeah, that was simple. So call them Enterobacterales, right?

Please stop. It’s an order!
**Beta-lactamases**
- Bacterial enzymes that inactivate β-lactam antibiotics by hydrolysis
- First penicillinase identified E coli 1940
- Inhibitor-resistant β-lactamases
- Chromosome (AmpC), plasmid (ESBL), transposable elements

**Beta-lactam antibiotics**
- Penicillins
- Cephalosporins
- Monobactams
- Carbapenems

**Beta-lactamase inhibitors**
- Clavulanic acid (only oral option, 1980s)
- Sulbactam
- Tazobactam
- Avibactam, Vaborbactam, Relebactam
Hydrolyze 3rd and 4th generation cephalosporins and monobactams Gram-negative rods, most commonly E. coli, Klebsiella pneumoniae, K. oxytoca, P. mirabilis CTX-M exploded in the 1990s and 2000s (first identified in a lab dog, then child in Munich (ceftriaxone, munich)

- hospital and community settings, the environment, the food supply and livestock
Hospitalization, antibiotic prophylaxis, recent antibiotic, +/- travel

Increasing incidence antibiotic resistant UTIs in pediatrics even without above risks over decade

3\textsuperscript{rd} gen cephalosporin resistance used to infer ESBL

- British Columbia 12% of 294 UTIs resistant 3\textsuperscript{rd} gen cephalosporin
- 3 fold increase community acquired ESBL UTI 2015 to 2021 Alabama (tertiary referral hospital)

**IMPACT OF CEFTRIAXONE RESISTANCE?**

Limits treatment options
ESBL most common mechanism, often coupled with resistance other antibiotic classes
(sulfonamides, aminoglycosides, fluoroquinolones)
Increased 90 day recurrence
### Preschools Uppsala, Sweden
- Diapers collected, 58 preschools 2016
- >6-fold increase ESBL compared to 2010
- 20% Cefotaxime resistant Enterobacteriaceae (67/334)
- 6 preschools ESBL carriage rate ≥40%
- 18 preschools no carriers

### Daycare Centers Netherlands, Belgium
- 28 Dutch (499 children), 18 Belgian (448 children) DCCs
- ESBL-E prevalence higher Belgium (16%)
- Antimicrobial use, hospitalizations less Netherlands
- Travel Asia previous 6 months associated with ESBL-E carriage but antibiotic use was not

### Vertical transmission, Israel
- Surveillance NICU over 1 year
- Mother rectal swab delivery room
- Infants NICU admit and twice weekly
- 478 infants, 409 mothers (313 screened)
- 21.4% mothers colonized, 14.8% infants
- 23 of 67 colonized mothers (34.3%) delivered 25 infants colonized with the same bacterial strain
- Colonized mother/infant more likely to be exposed to antibiotics during pregnancy and delivery than colonized mothers with non-colonized infants
- 4 of 71 colonized infants LOS with ESBL, 2 died
New Resistant Bacteria

Selective Pressure → Upregulation of resistance factors or novel mutations

Susceptible Bacteria

Some selective pressures
- Agriculture
- Growth promotion
- 80% US antibiotic use
- Clinicians and patients
- Patient satisfaction models
- Health system administration
- Payment and reimbursement models
- Supply chain
- COVID
COVID-19 CREATED A PERFECT STORM
The U.S. lost progress combating antimicrobial resistance in 2020

↑15% Antimicrobial-resistant infections and deaths increased in hospitals in 2020.

~80% Patients hospitalized with COVID-19 who received an antibiotic March-October 2020.

⚠ Delayed or unavailable data, leading to resistant infections spreading undetected and untreated.

INVEST IN PREVENTION.

Setbacks to fighting antimicrobial resistance can and must be temporary.

Learn more: https://www.cdc.gov/drugresistance/covid19.html
FIGHT ANTIMICROBIAL RESISTANCE WITH INFECTION CONTROL

As a frontline healthcare worker, you play an important role in fighting antimicrobial resistance.

When you practice infection control, you stop resistant germs from:

- Entering the body and causing infections through procedures and medical devices
- Spreading to people from surfaces like bedrails or the hands of healthcare workers
- Moving with patients when they are transferred between facilities
- Spreading into the community, making them harder to control

Preventing new health care associated infections
Stopping the spread of resistant organisms
Reducing the need for antibiotics

https://www.cdc.gov/infectioncontrol/projectfirstline/
HEALTHCARE PROVIDERS: ACTIONS TO COMBAT RESISTANCE

Prevent infections and spread

Antimicrobial prescribing

Outpatient, inpatient antibiotic stewardship (health system support)
Treatment guidelines
Appropriate diagnostic tests

Be alert and take action

Maine Health Alert Network (HAN) System

PUBLIC HEALTH ADVISORY

Local antibiogram
Critical lab value calls
Maine CDC notifiable diseases and conditions list
Watchful Waiting for Ear Infections

What is an ear infection?
There are different types of ear infections. Middle ear infection (acute otitis media) is an infection in the middle ear, or behind the eardrum.

What does the term “watchful waiting” mean?
It means observing your child for 2-3 days to give your child’s immune system time to fight off the infection rather than starting antibiotics immediately. Your healthcare professional will wait to see if your child gets better before giving your child a prescription for antibiotics.

Why would my healthcare professional recommend watchful waiting instead of giving antibiotics immediately?
Studies have shown that most children with mild ear infections get better without antibiotics. The child’s immune system is often able to fight off the infection on its own. Antibiotics can sometimes improve symptoms more quickly, but antibiotics can also cause problems, such as side effects and antibiotic resistance. Two out of 3 children with mild ear infections get better without receiving any antibiotics.

Which children qualify for watchful waiting?
Children between ages 6 months and 23 months if only one ear is infected, and who have:

- Symptoms of ear infection that have lasted less than 2 days.
- Mild ear pain
- Temperature lower than 102.2°F (39°C)

OR Children ages 2 years and older if one or both ears are infected, and who have:

How can I improve my child’s symptoms if I don’t give antibiotics?
The symptoms of an ear infection—like ear pain and fever—can be helped with ibuprofen or acetaminophen, rest, and extra fluids.

To learn more about antibiotic prescribing and use, visit www.cdc.gov/antibiotic-use or call 1-800-CDC-INFO.
72% of antibiotic prescriptions are likely necessary. (But we still need to improve drug selection, dose and duration)

At least 28% of antibiotic prescriptions are unnecessary. In U.S Doctor’s Offices and EDs

Learn more at cdc.gov/antibiotic-use.
Shorter antibiotic course for ventilator associated tracheitis was not associated with subsequent development of pneumonia. Longer course was associated with increased MDRO colonization (38% vs 8%).

**Figure 2.** Cumulative distribution function of hospital-acquired pneumonia (HAP), shown for 118 children who met the definition of ventilator-associated tracheitis (VAT). $P = .46$, by log-rank test.

**Figure 3.** Cumulative distribution function of colonization or infection with a multidrug-resistant organism (MDRO), shown for 150 children receiving antibiotic therapy for ventilator-associated tracheitis (VAT). $P \leq .01$, by log-rank test.

2016 NEJM trail 5 days amoxicillin-clavulanate for otitis media in those 6-23 months of age associated with increased treatment failure (34% vs 16%). 10 days was not associated with nasopharyngeal colonization with penicillin resistant pathogens (Strep pneumo and H flu). N=520
France (FR) and Spain (ES)
Higher rate antibiotic resistance with higher consumption

n=19
z=0.84 (0.62–0.94)
p<0.0001
Streptococcus pneumoniae resistance data delay

New vaccines will be critical for *S. pneumoniae* as resistance to some important antibiotics continues to increase.*

NorDx 2023 42% erythromycin

<table>
<thead>
<tr>
<th>% resistant to select antibiotics</th>
<th>32%</th>
<th>22%</th>
<th>8%</th>
<th>4%</th>
</tr>
</thead>
<tbody>
<tr>
<td>% resistant to erythromycin</td>
<td>40%</td>
<td>30%</td>
<td>20%</td>
<td>10%</td>
</tr>
</tbody>
</table>


*Unable to compare data with 2019 report estimates, see Methods for details.

Streptococcus pyogenes

GAS resistance was already on the rise, emphasizing the need for antibiotic stewardship—especially for patients with viral infections like COVID-19 that are not treatable with antibiotics.

<table>
<thead>
<tr>
<th>% resistant to erythromycin</th>
<th>12%</th>
<th>24%</th>
<th>25%</th>
</tr>
</thead>
<tbody>
<tr>
<td>% resistant to clindamycin</td>
<td>9%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Primary Care, England
Patients were less satisfied in practices with frugal antibiotic prescribing
Patient surveys 2012
-2.7 million questionnaires, 982,999 responses; response rate 36%
-Practice antibiotic prescribing volumes

Primary Care, California
50% parents previsit expectation antibiotics for URI
Age 2-10 yo, 287 encounters, 10 physicians
Pre and post visit surveys, visit audiotaped (transcribed and coded)
Higher satisfaction if contingency plan given when no prescription
<table>
<thead>
<tr>
<th>Common Respiratory Infections</th>
<th>Common Cause</th>
<th>Are Antibiotics Needed?*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common cold/runny nose</td>
<td>Virus</td>
<td>No</td>
</tr>
<tr>
<td>Sore throat (except strep)</td>
<td>Virus</td>
<td>No</td>
</tr>
<tr>
<td>COVID-19</td>
<td>Virus</td>
<td>No</td>
</tr>
<tr>
<td>Flu</td>
<td>Virus</td>
<td>No</td>
</tr>
<tr>
<td>Bronchitis/chest cold (in otherwise healthy children and adults)</td>
<td>Virus</td>
<td>No**</td>
</tr>
<tr>
<td>Middle ear infection</td>
<td>Virus</td>
<td>Maybe</td>
</tr>
<tr>
<td>Sinus infection</td>
<td>Virus</td>
<td>Maybe</td>
</tr>
<tr>
<td>Strep throat</td>
<td>Virus</td>
<td>Yes</td>
</tr>
<tr>
<td>Whooping cough</td>
<td>Virus</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Antiviral drugs are available for some viral infections, such as COVID-19 or flu.

**Studies show that in otherwise healthy children and adults, antibiotics for bronchitis won’t help patients feel better.

To learn more about antibiotic prescribing and use, visit www.cdc.gov/antibiotic-use.
Antibiotic Shortages Are Fueling Antimicrobial Resistance

In countries worldwide, shortages of first-line antibiotics often lead to overuse of those that are specialized or kept in reserve for emergencies. Not only may these substitutes be less effective, but reliance on them increases the risk of drug resistance developing and infections becoming more difficult to treat in the long run.

24 November 2023 • 4 min read by Project Syndicate
World-first scheme underway to tackle AMR and protect UK patients

A pioneering scheme to provide new antibiotics to NHS patients by offering to pay pharmaceutical companies upfront for their work will start...

Jun 17, 2020

NEWS RELEASE
June 5, 2019

DISARM Act Provides Framework Needed to Spur Antibiotic R&D, Protect Existing Drugs

PASTEUR (Pioneering Antimicrobial Subscriptions to End Upsurging Resistance) Act (introduced 4/2023)
delink companies' profits from the volume of antibiotics sold
WE ARE CONNECTED

STOP ANTIBIOTIC RESISTANCE NOW

Antibiotic Resistance is driven by a wide variety of factors, ranging from contaminated bodies of water to misuse of antibiotics in food production and human medicine.

PROTECT YOUR COMMUNITY
KNOW THE FACTS

www.cdc.gov/DrugResistance

BECOME A STOP ANTIBIOTIC RESISTANCE NOW CAMPAIGN AMBASSADOR TODAY
Tyson chicken in 2017 “No antibiotics ever”, 2023 “No antibiotics important to human medicine”

- Restarting use ionophores for coccidia protozoal parasite but a study has shown presence of resistance genes for the ionophore salinomycin was correlated with the presence of resistance genes for erythromycin, tetracycline, and ampicillin, which are designated as medically important antibiotics.
Herbicides promotes antibiotic resistance in soil microbiomes
Great Britian higher antibiotic resistant bacteria rural vs urban

Seagulls: Pooping Resistant Bacteria on Your Beach
Resistance factors – the mutations that allow bacteria to defend themselves against the attack of antibiotics – spread around the world in...

Air pollution may contribute to rising threat of antimicrobial resistance, study says
By Jen Christensen, CNN
Published 6:30 PM EDT, Mon August 7, 2023
Changing Susceptibility of Staphylococcus aureus in a US Pediatric Population

Percent of Staphylococcus aureus isolates susceptible to oxacillin by US region, 2005–2014
>100,000 CFU/mL gram negative rod. Testing indicates that this isolate produces and extended spectrum beta lactamase. This organism is resistant to all penicillins, cephalosporins and aztreonam. Escherichia coli **ESBL Producer**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Susceptibility</th>
<th>MIC (mcg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>Sensitive</td>
<td>&lt;=8</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Resistant</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Ampicillin/sulbactam</td>
<td>Sensitive</td>
<td>8/4</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>Resistant</td>
<td></td>
</tr>
<tr>
<td>Cefazolin</td>
<td>Resistant</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Cefepime</td>
<td>Resistant</td>
<td></td>
</tr>
<tr>
<td>Ceftriazone</td>
<td>Resistant</td>
<td>&gt;32</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>Sensitive</td>
<td>&lt;=0.25</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Sensitive</td>
<td>&lt;=2</td>
</tr>
<tr>
<td>Meropenem</td>
<td>Sensitive</td>
<td>&lt;=0.5</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Sensitive</td>
<td>&lt;=16</td>
</tr>
<tr>
<td>Piperacillin+Tazobactam</td>
<td>Sensitive</td>
<td>&lt;=2/4</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Sensitive</td>
<td>&lt;=2</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>Sensitive</td>
<td>&lt;=2</td>
</tr>
<tr>
<td>Trimethoprim+Sulfamethoxazole</td>
<td>Sensitive</td>
<td>&lt;=0.5</td>
</tr>
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Change cephalexin to ........?
>100,000 CFU/mL gram negative rod. Testing indicates that this isolate produces and extended spectrum beta lactamase. This organism is resistant to all penicillins, cephalosporins and aztreonam. 

**Escherichia coli **ESBL Producer

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<td>Resistant</td>
<td>&gt;16 mcg/mL</td>
</tr>
<tr>
<td>Ampicillin/sulbactam</td>
<td>Resistant</td>
<td>&gt;16/8 mcg/mL</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>Resistant</td>
<td></td>
</tr>
<tr>
<td>Cefazolin</td>
<td>Resistant</td>
<td>&gt;16 mcg/mL</td>
</tr>
<tr>
<td>Cefepime</td>
<td>Resistant</td>
<td></td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>Resistant</td>
<td></td>
</tr>
<tr>
<td>Ceftriazone</td>
<td>Resistant</td>
<td>32 mcg/mL</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Resistant</td>
<td>&gt;2 mcg/mL</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>Sensitive</td>
<td>&lt;=0.25 mcg/mL</td>
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<tr>
<td>Gentamicin</td>
<td>Sensitive</td>
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<td>&lt;=16 mcg/mL</td>
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<td>Piperacillin + Tazobactam</td>
<td>Sensitive</td>
<td>16/4 mcg/mL</td>
</tr>
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<td>Tetracycline</td>
<td>Resistant</td>
<td>&gt;8 mcg/mL</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>Resistant</td>
<td>&gt;8 mcg/mL</td>
</tr>
<tr>
<td>Trimethoprim + Sulfamethoxazole</td>
<td>Resistant</td>
<td>&gt;2/38 mcg/mL</td>
</tr>
</tbody>
</table>

**What to start as does not want longer course nitrofurantoin?**
WHAT ABOUT A 5 YO MALE WITH FEVER, VOMITING, DIARRHEA?

Urine culture outside hospital >100,000 CFU/mL ESBL E coli
Susceptible: ciprofloxacin, nitrofurantoin, amikacin, zosyn, ertapenem, levofloxacin, meropenem, tetracycline, cefoxitin, tobramycin

Prescribed nitrofurantoin but could not get liquid for 3 days so sent to outside ED. UA and urine culture requested but was after 2 doses meropenem (initial urine culture into hat, no UA)

Admission UA (3 days post initial presentation) negative nitrite/leuks +ketones. Fever, diarrhea improved, vomiting resolved prior to antibiotic. Entire household had less than 24 hours vomiting +/- diarrhea.

Treatment?

WHAT ABOUT A 17 YO FEMALE WITH HEADACHE, LOW BACK PAIN, ABDOMINAL PAIN, FEVER?

UA positive leuk, negative nitrite
Started Bactrim
UCX ESBL E coli resistant to Bactrim, levofloxacin (still symptomatic)
Started meropenem, discharged with ertapenem via midline to complete 10 days
CVA tenderness improving time of discharge (CRP 137.5 mg/L to 59.2)

Seeing increased community acquired ESBL UTIs, do we need to alter empiric therapy?
NO: TIME TO APYREXIA WITH EXTENDED-SPECTRUM \( \beta \)-LACTAMASES (ESBLs) FEBRILE UTI

- Effective Initial antibiotic therapy
- Ineffective Initial antibiotic therapy

\[ p = 0.38 \]
ONE HEALTH

SAVE OUR FUTURE

one earth

SAVE THE PLANET

Questions?


REFERENCES


IMAGES

Canva