Diagnostic Solutions laboratory

GI-MAP® GI Microbial Assay Plus

UNDERSTANDING AND OVERCOMING ANTIBIOTIC RESISTANCE IN THE GI TRACT

Introduction: Recently, Dr. Amy Rolfsen, presented a webinar on the antibiotic resistance (AR) genes evaluated on the GI-MAP® (GI-Microbial Assay Plus). In the webinar, Dr. Rolfsen explains how to interpret the AR genes and introduces the concept of natural synergists to overcome bacterial resistance mechanisms. The following handout outlines the topics covered and is meant to be a companion piece to her original presentation.

Presented by Amy Rolfsen, ND, on December 18, 2019
Watch the webinar at: https://www.diagnosticsolutionslab.com/webinars/understanding-and-overcoming-antibiotic-resistance-gi-tract

UAR-GI-1219r1

WHAT IS ANTIBIOTIC RESISTANCE?

Antibiotic resistance is when bacteria develop the ability to survive the antibiotics that they are meant to be susceptible to.

- Antibiotics are designed to kill bacteria
- Bacteria have found ways to avoid being killed by bacteria
- Misuse of antibiotics can select for resistant strains

CDC THREAT REPORT 2019

"Stop relying *only* on new antibiotics" – Dr. Robert Redfield (CDC)

STATS

- ~ 3 million AR infections annually in the US
- Resulting in ~ 45000+ deaths
- Decrease of 18% since 2013
- (stats include *C. difficile* infection)

NEW ANTIBIOTICS

- 42 new antibiotics in development
  - ¼ of which have a new MOA
  - 11 of which may address urgent AR threats
- 5 step process to approval

CDC RECOMMENDS:

- Test for resistance before giving antibiotics
- Finding alternatives to antibiotics

THERAPEUTIC TARGETS FOR BOTANICAL TREATMENT:

- Efflux pumps
- Quorum sensing
- Bacterial adhesion
- Cell membrane permeability
- Bacterial DNA
- Enzymes
- Biofilms

TESTING FOR ANTIBIOTIC RESISTANCE WITH THE GI MAP

- Improves accuracy of diagnosis
- Helps with antibiotic selection
- Avoids inappropriate antibiotic use
- Helps identify the spread of AR bacteria

ANTIBIOTIC RESISTANCE MARKERS ON THE GI MAP

- 13 Helicobacter genes
  - These markers are specific to *Helicobacter*
- 22 Universal Microbiota genes
  - These genes are easily transferred between organisms, so they are presented as “universal” genes instead of individual species
- Markers selected to be:
  - Clinically relevant
  - Well researched
- Dynamic – these markers will change based on microbiome

USING QUANTITATIVE PCR

- Allows you to identify large colonies
- Use in the context of clinical history
  - Frequent infections with the same organism
  - Recent antibiotic use

ORGANISMS ON THE GI MAP THAT ARE REPORTED TO HAVE ANTIBIOTIC RESISTANCE:

All of the following organism have the potential to produce biofilms.

Gram Positive

- *Clostridium* spp.
- *Enterococcus*
- *Lactobacillus*
- *Bacillus*
- *Staphylococcus*
- *Streptococcus*

Gram Negative

- *Campylobacter*
- *Escherichia*
- *Salmonella*
- *Vibrio cholera*
- *Yersinia enterocolitica*
- *Helicobacter*
- *Bacteroides*
- *Enterobacter*
- *Morganella*
- *Pseudomonas*
- *Citrobacter*
- *Klebsiella*
- *M. avium - paratuberculosis*
- *Prevotella*
- *Proteus*
- *Fusobacterium*

Other

- *Candida*

STRATEGIES TO OVERCOME RESISTANCE

1. **Antibiotic stewardship**
   - Reserve ABX for serious infections
   - Choose ABX appropriately
     - Test for resistance/susceptibility
     - Narrowest spectrum possible
   - Encourage proper use in patients
     - Avoid use of ABX in viral infections
     - Educate patients about appropriate course of treatment
   - Improve efficacy of antibiotics (AKA. Combine with botanicals)

2. **Substitute ABX with botanicals**
   - Berberine-containing plants (Mahonia, Hydrastis, Coptis etc.)
   - Garlic
   - Artemisia
   - Oregano
   - Usnea
   - Neem

3. Combine ABX/Antimicrobials with synergists

Efflux Pump Inhibitors

- Artemesia
- Berberis/Mahonia
- Bitter orange
- Calamus
- Chinese Skullcap
- Cinnamon
- Geranium
- Ginger
- Gotu Kola
- Grapefruit oil
- Green Tea
- Honeysuckle
- Licorice
- Milk Thistle
- Myrrh
- Nootka Cypress Cone
- Pomegranate
- Quercetin
- Rosemary

Quorum Sensing Inhibitors

- Basil
- Berberis/Mahonia
- Berries
- Curcumin
- Garlic
- Ginger
- Grapefruit juice
- Green Tea
- Kale
- Quercetin
- Rosemary
- Thyme

Adhesion Inhibitors

- Berberis/Mahonia
- Catnip
- Cranberry
- Green Tea
- Licorice

Cell Wall Disruptors

- Berberis/Mahonia
- Berries
- Curcumin
- Dog Rose
- Hops
- Nootka Cypress Cone
- Thyme
- Usnea

Enzyme inhibitors

- ß lactamase
  - Calamus
  - Chinese skullcap
  - Garlic
  - Green tea
- DNA Synthase
  - Resveratrol
  - Garlic
- Acetylcholinesterase
  - Tansy

Biofilm Disruptors

- Berberis/Mahonia
- Cinnamon
- Clove
- Curcumin
- Ginger
- Grapefruit juice
- Green tea
- Lemongrass
- Licorice
- Quercetin
- Resveratrol
- Black Cumin
- Enzymes
- Thiols (NAC, ALA, glutathione)
- Many, many others

4. Support the immunity & terrain

Immune Support: Natural Products

- Colostrum
- Immunoglobulins
- Mushrooms
- Astragalus
- Elderberry
- Echinacea
- Andrographis

Immune Support: Lifestyle

- Stress
- Outlook: positivity, humor
- Sleep
- Exercise/Movement
- Social support

Dietary Considerations

- Whole foods diet: Eat each color of the rainbow daily
  - Polyphenols
  - Myricetin
  - Gallic Acid
  - Kale & Berries
  - Increase water intake
  - Green tea
  - Fresh garlic
  - Culinary Herbs and spices: cinnamon, cloves, ginger, rosemary, thyme, oregano, black pepper
  - Decrease sugar and simple carbohydrates

RESOURCES:

CDC CURRENT THREATS 2019

Urgent Threats:

- Carbapenem-resistant *Acinetobacter*
- *Candida auris*
- *Clostridioides difficile*
- Carbapenem-resistant *Enterobacteriaceae*
- Drug-resistant *Neisseria gonorrhoeae*

Serious Threats:

- Drug-resistant *Campylobacter*
- Drug-resistant *Candida*
- Extended-spectrum beta-lactamase-producing Enterobacteriaceae
- Vancomycin-resistant *Enterococci*
- Multidrug-resistant *Pseudomonas aeruginosa*
- Drug-resistant nontyphoidal *Salmonella*
- Drug-resistant *Salmonella* serotype Typhi
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus*
- Drug-resistant *Streptococcus pneumoniae*
- Drug-resistant Tuberculosis

Concerning Threats

- Erythromycin-resistant group A *Streptococcus*
- Clindamycin-resistant group B *Streptococcus*

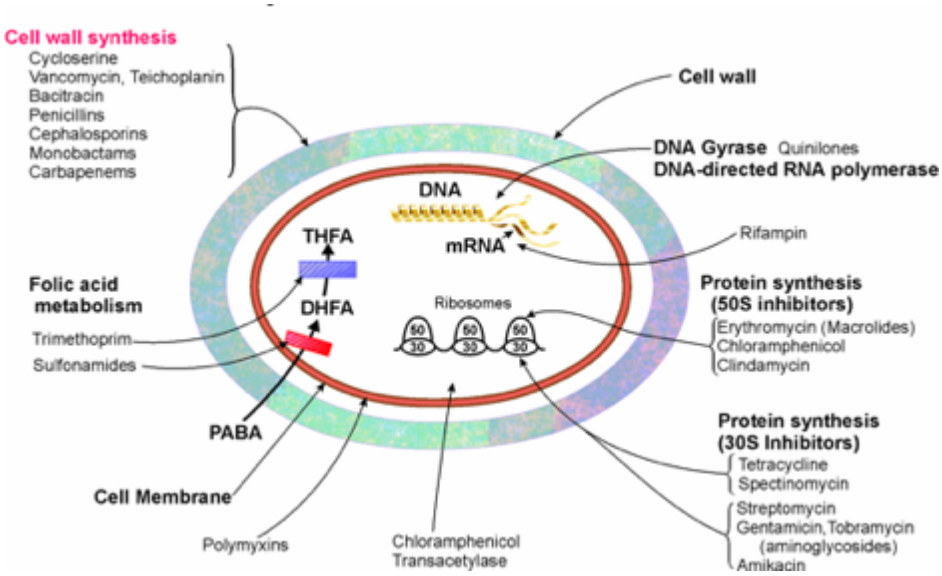
Watch List

- Azole-resistant *Aspergillus fumigatus*
- Drug-resistant *Mycoplasma genitalium*
- Drug-resistant *Bordetella pertussis*

UNIVERSAL AR MARKERS ON THE GI MAP

Gene ID	Resistance mechanism	Found in (GI relevent)
CTX-M-3	Antibiotic inactivation (β-lactamase)	*Citrobacter, Enterobacter, Escherichia, Shigella* spp
CTX-M-14 (Toho-3)	Antibiotic inactivation (β-lactamase)	*Citrobacter, Enterobacter, Escherichia, Kelbsiella, Proteus, Salmonella, Shigella, Vibrio*
CTX-M-35 (cephalosporin)	Antibiotic inactivation (β-lactamase)	*Citrobacter*
CTX-M-63	Antibiotic inactivation (β-lactamase)	*Salmonella*
GES-3	Antibiotic inactivation (β-lactamase)	*Klebsiella*
NDM-1	Antibiotic inactivation (β-lactamase)	*Citrobacter, Enterobacter, Escherichia, Klebsiella, Morganella, Proteus, Shigella, Vibrio*
OXA-30	Antibiotic inactivation (β-lactamase)	*Citrobacter, Enterobacter, Escherichia, Kelbsiella, Morganella, Proteus, Salmonella, Shigella*
PER-1	Antibiotic inactivation (β-lactamase)	*Proteus*
PER-2	Antibiotic inactivation (β-lactamase)	*Citrobacter, Salmonella*
SHV-24	Antibiotic inactivation (β-lactamase)	*Escherichia*
TEM-70	Antibiotic inactivation (β-lactamase)	*Escherichia, Vibrio*
VEB-1	Antibiotic inactivation (β-lactamase)	*Escherichia, Pseudomonas, Enterobacter*
qnrA	Block drug binding to target protein	*Citrobacter, Enterobacter, Klebsiella, Salmonella*
qnrB	Block drug binding to target protein	*Citrobacter, Enterobacter, Escherichia, Klebsiella, Morganella*
ermA		*Enterococcus, Staphylococcus*
ermB	Inducible methylation of ribosomal target (MLSB phenoytpe)	*Enterococcus, Campylobacter, Clostridium, Escherichia, Shigella, Staphylococcus, Streptococcus, Vibrio*
emrC		*Staphylococcus*
mefE	efflux pump	*Streptococcus*
vanA	Block drug binding to target protein	*Enterococcus, Staphylococcus, Klebsiella, Pseudomonas, Mycobacterium*
vanB	Block drug binding to target protein	*Enterococcus*
vanC	Block drug binding to target protein	*Enterococcus*

BACTERIAL TARGETS BY ANTIBIOTIC CLASS (CHANDA & KALPNA 2011)



ENZYMES THAT TARGET ANTIBIOTICS BY CLASS:

- ß lactams (penicillins, cephalosporins, carbapenems, monobactams) – ß lactamases
- Lincosamides – nucleotidyltransferases
- Aminoglycosides – phosphotransferases, nucleotidyltransferases, acetyltransferases
- Phosphomycin – phosphotransferases, epoxide hydrolases, s-transferases
- Macrolides – phosphotransferases, glycosyltransferases, esterases
- Streptogramin A – acetyltransferases
- Phenicols – acetyltransferases, hydrolases
- Fluoroquinolones – acetyltransferases
- Tetracyclines – monooxygenases

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