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SYLLABUS

67TH Annual Scientific Assembly

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WEST VIRGINIA ACADEMY OF FAMILY PHYSICIANS
STRONG MEDICINE FOR WEST VIRGINIA
Case Studies in Type 2 Diabetes Mellitus: Focus on Cardiovascular Outcomes Trials

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Disclosures
Michael Cobble, MD, FNLA, has disclosed that he is a consultant to Kowa, as well as on the speaker’s bureau for Amarin, Amgen, Astra Zeneca, Kowa, and Sanofi.

Gregory Scott, PharmD, RPh, Editorial Support, has no real or apparent conflicts of interest to report.
Learning Objectives
After participating in this symposium, the learner will be able to:
- Characterize type 2 diabetes as a cardiovascular risk factor
- Differentiate traditional clinical outcomes trials from cardiovascular outcome trials
- Describe the results of cardiovascular outcome trials regarding cardiovascular safety
- Describe the results of cardiovascular outcome trials regarding cardiovascular benefit
- Integrate all available evidence, guideline recommendations, and approved product labeling in individualizing therapy

In patients with type 2 diabetes mellitus, the primary treatment goal is to control/reduce:
1. Blood glucose
2. Blood lipid
3. Blood pressure
4. Cardiovascular risk

The goal of cardiovascular safety trials is to demonstrate that the CV safety of the new therapy is
1. similar to placebo
2. similar to metformin
3. superior to placebo
4. superior to metformin

Medications in which two classes have been shown to reduce the risk of cardiovascular events compared to placebo as part of standard care?
1. Sulfonylurea and DPP-4i
2. DPP-4i and SGLT-2i
3. SGLT-2i and GLP-1RA
4. GLP-1RA and meglitinide

Diabetes Mellitus as a Cardiovascular Risk Factor
Framingham Heart Study

In patients with type 2 diabetes mellitus, the primary treatment goal is to control/reduce:
1. Blood glucose
2. Blood lipid
3. Blood pressure
4. Cardiovascular risk
UKPDS: 1% HbA1c Decrease and Reduced Risk of Complications

<table>
<thead>
<tr>
<th>Decrease</th>
<th>Decrease</th>
<th>Decrease</th>
<th>Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microvascular disease</td>
<td>Lower-extremity amputation or fatal peripheral vascular disease</td>
<td>MI or stroke</td>
<td>Myocardial infarction</td>
</tr>
</tbody>
</table>

*UKPDS, United Kingdom Prospective Diabetes Study

Recommended Targets for Adults with T2DM

<table>
<thead>
<tr>
<th>ADA</th>
<th>AACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>≤ 7.0%&lt;br&gt;≤ 6.5% (Individuals)</td>
</tr>
<tr>
<td>Pre-prandial plasma glucose</td>
<td>≤ 80–130 mg/dL&lt;br&gt;≤ 100 mg/dL</td>
</tr>
<tr>
<td>Peak post-prandial glucose</td>
<td>≤ 180 mg/dL&lt;br&gt;≤ 140 mg/dL</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≤ 140/90 mm Hg&lt;br&gt;≤ 120/80 mm Hg</td>
</tr>
<tr>
<td>LDL Cholesterol</td>
<td>≤ 100 mg/dL&lt;br&gt;≤ 100 mg/dL (high-risk)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≤ 150 mg/dL&lt;br&gt;≤ 150 mg/dL</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>≥ 40 mg/dL (male)&lt;br&gt;≥ 50 mg/dL (female)</td>
</tr>
</tbody>
</table>

*Values are lower extremity amputation, or fatal peripheral vascular disease definitions are by sex and age. Patients should be treated based on their individual conditions, and include diabetes control. Pre-diabetic and T2DM are not to be treated as equal. HbA1c measurement should be used within the beginning of the meal, gastric bypass can lead to T2DM.

Approach to the Management of Hyperglycemia

<table>
<thead>
<tr>
<th>Patient/Disease Features</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>microvascular damage</td>
<td>≤ 1%</td>
</tr>
<tr>
<td>Risk of hypoglycemia and adverse effects</td>
<td>≤ 5%</td>
</tr>
<tr>
<td>Disease History</td>
<td>Never</td>
</tr>
<tr>
<td>Life expectancy</td>
<td>Long</td>
</tr>
<tr>
<td>Impaired consciousness</td>
<td>None</td>
</tr>
<tr>
<td>Establish severe complications</td>
<td>None</td>
</tr>
<tr>
<td>Patient attitude &amp; medication adherence</td>
<td>90%</td>
</tr>
<tr>
<td>Resource availability</td>
<td>80%</td>
</tr>
</tbody>
</table>

Comprehensive Management of Diabetes

Treating patients with T2DM is more than blood glucose control

**There’s also:**
- Antiplatelet therapy
- Blood pressure
- Cholesterol
- Dietary changes
- Exercise changes

**And let’s not forget:**
- Smoking
- Weight
- Regular examination of
  - Eyes
  - Mouth/Teeth
  - Feet/Skin
  - Kidneys

**Plus:**
- Diabetes distress

Type 2 Diabetes Mellitus

- Type 2 diabetes mellitus is a
  - chronic, progressive disease
- That requires
  - ongoing collaboration, education, and support
- To help patients
  - improve self-management
- With the goal of
  - reducing cardiovascular risk and improving health outcomes

Case Scenario: Rafael

- 62 yo man diagnosed with T2DM 4 months ago (HbA1c 8.6%)
- 3-y history of LDL hyperlipidemia, hypertriglyceridemia
- Lifestyle + Metformin initiated 4 mos ago

**Currently:**
- A1c 7.5%
- BMI 31.4 kg/m²
- BP 134/88 mm Hg
- LDL-C 114 mg/dL
- Triglycerides 320 mg/dL

**Medications:**
- Metformin 1 g BID
- HCTZ 25 mg QD
- Enalapril 10 mg BID
- Simvastatin 20 mg QD
- ASA 81 mg QD
Was metformin monotherapy the appropriate initial treatment for Rafael's hyperglycemia?

1. Yes
2. No
3. It depends

Since Rafael has a HbA1c of 7.5%, which class of medication would you add to metformin?

1. DPP-4i
2. GLP-1RA
3. SGLT-2i
4. Sulfonylurea
5. Thiazolidinedione
Antihyperglycemic Agents as Add-on to Metformin: Effect on HbA1c

Effect of GLP-1 Agonists and SGLT-2 inhibitors on HbA1c

Which of the following do you consider to be the most important in selecting further glucose-lowering treatment for Rafael?
1. Glucose-lowering efficacy
2. Risk of hypoglycemia
3. Impact on weight
4. Cardiovascular safety/benefit
5. Barriers to adherence

Risk of Cardiovascular Outcomes: Meta-analysis of 42 Randomized Controlled Trials

Impact of Pioglitazone on Macrovascular Disease: PROactive

- 5238 patients with T2DM with macrovascular disease
- Randomized to:
  - Pioglitazone 15-45 mg/d
  - Placebo
  - Continue baseline therapy
- Mean follow-up 34.5 months

FDA Diabetes Mellitus Guidance - 2008

Guidance for Industry

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

- Provides recommendations about how to demonstrate that a new antidiabetic therapy to treat T2DM is not associated with an unacceptable increase in CV risk
- That is, the new therapy is safe (noninferior to placebo)
- It is also possible to demonstrate that the new therapy offers CV benefit
- Assess major adverse CV events
  - CV death, nonfatal MI, nonfatal stroke
  - Other events possible
- Trial(s) should:
  - include patients with T2DM at higher risk of CV events
  - Advanced disease, advanced age, renal impairment
  - be ≥ 2 years in duration
Traditional Clinical Outcome Trial vs Diabetes Medication CV Safety Trial

- Traditional clinical outcome trial
  - CV risk of new treatment is significantly less than comparator, ie, offers CV benefit
- Diabetes medication safety trial
  - CV risk of new treatment is non-inferior (similar) to placebo
  - If non-inferiority is demonstrated, the possible superiority (ie, CV benefit) of new treatment can be assessed

The goal of cardiovascular safety trials is to demonstrate that the CV safety of the new therapy is

1. similar to placebo
2. similar to metformin
3. superior to placebo
4. superior to metformin

Nomenclature

- Primary end point:
  - Composite of: CV death, non-fatal MI, and non-fatal stroke
  - Heart failure hospitalization
  - All cause death
    - Total number of deaths due to that condition during a specific time, Death from any cause.

Nomenclature (cont)

- Non-inferiority: No increase in CV risk compared to placebo
  - Superiority: If non-inferiority is demonstrated, can look for superiority
    - CV risk significantly reduced compared to placebo

Diabetes Medication CV Safety Trials

<table>
<thead>
<tr>
<th>Medication</th>
<th>DPP-4</th>
<th>GLP-1 RA</th>
<th>SGLT-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alogliptin</td>
<td>EXAMINE</td>
<td>Albiglutide</td>
<td>CANVAS</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>CARAMELINA</td>
<td>Exenatide</td>
<td>CANVAS-R</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>SAVER</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>TECOS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Medications Whose CV Safety Has Been Shown to Be Non-Inferior to Placebo

<table>
<thead>
<tr>
<th>Class</th>
<th>DPP-4 Inhibitors</th>
<th>GLP-1 Receptor Agonists</th>
<th>SGLT-2 Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alogliptin</td>
<td>Exenatide GLP-1</td>
<td>Canagliflozin</td>
<td></td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>Linagliptide</td>
<td>Dapagliflozin</td>
<td></td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>Lixisenatide</td>
<td>Empagliflozin</td>
<td></td>
</tr>
</tbody>
</table>

References:
Case Scenario: Rafael
- 62 yo man diagnosed with T2DM 4 months ago (HbA1c 8.6%)
- Lifestyle + Metformin → HbA1c 7.5%
- BMI 31.4 kg/m²
- BP 134/86 mmHg
- LDL-C 114 mg/dL
- Triglycerides 320 mg/dL
- Medications
  - Metformin 1 g BID
  - HCTZ 25 mg QD
  - Enalapril 10 mg BID
  - Simvastatin 20 mg QD
  - ASA 81 mg QD

Which class of medication would you add to metformin?
1. DPP-4i
2. GLP-1RA
3. SGLT-2i
4. Sulfonylurea
5. Thiazolidinedione

Case Scenario: Julie
- 69 yo woman diagnosed with T2DM 3 years ago (HbA1c 9.4%)
  when she suffered a myocardial infarction
- Lifestyle + Metformin + SU → HbA1c 6.9% (now 7.7%)
- BMI 36.8 kg/m² → 31.2 kg/m²
- BP 130/78 mmHg
- eGFR 63 mL/min/1.73 m²
- LDL-C 64 mg/dL
- Triglycerides 156 mg/dL
- Medications
  - Metformin 1 g BID
  - Glimepiride 6 mg QD
  - Lisinopril/HCTZ 20 mg/25 mg QD
  - Atorvastatin 60 mg QD
  - ASA 81 mg QD

Case Scenario: Julie
- Adherence with glimepiride has been poor since she experienced a severe hypoglycemia
  episode 7 months ago
  - Has experienced several episodes of asymptomatic hypoglycemia since
  - HbA1c has risen over the past year (now 7.7%)
- Plan
  - Discontinue glimepiride
  - Start another medication

Which class of medication would you add to metformin?
1. DPP-4i
2. GLP-1RA
3. SGLT-2i
4. Thiazolidinedione

Antihyperglycemic Medications Demonstrating Cardiovascular Benefit: SGLT-2 Inhibitors

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Rate/100 patient-years</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, nonfatal MI, nonfatal stroke*</td>
<td>3.09</td>
<td>1.35 (0.80 - 2.25)</td>
</tr>
<tr>
<td>MI hospitalization</td>
<td>0.55</td>
<td>0.87 (0.47 - 1.70)</td>
</tr>
<tr>
<td>CV death or MI hospitalization</td>
<td>1.65</td>
<td>2.08 (1.08 - 4.04)</td>
</tr>
<tr>
<td>Progression of albuminuria</td>
<td>0.94</td>
<td>12.87 (7.33 - 22.04)</td>
</tr>
<tr>
<td>45% reduction eGFR, renal death or transplantation, renal death</td>
<td>0.55</td>
<td>1.50 (0.40 - 5.74)</td>
</tr>
</tbody>
</table>

CV, cardiovascular; eGFR, estimated glomerular filtration rate; MI, heart attack; MI, myocardial infarction

*Primary endpoint
Antihyperglycemic Medications Demonstrating Cardiovascular Benefit: SGLT-2 Inhibitors (cont)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rate/100 patient-years</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empagliflozin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death, nonfatal MI, nonfatal stroke</td>
<td>2.26</td>
<td>1.47</td>
</tr>
<tr>
<td>CV death or HF hospitalization</td>
<td>1.34</td>
<td>1.41</td>
</tr>
<tr>
<td>HF hospitalization</td>
<td>0.62</td>
<td>0.85</td>
</tr>
</tbody>
</table>

240 mg decrease in eGFR to <45 mL/min/1.73 m², or death from renal or CV cause |

CV: cardiovascular; MI: myocardial infarction; HF: heart failure; MI: myocardial infarction; eGFR: estimated glomerular filtration rate. 

Source: ACC/AHA 2013 MACE-3 results.

Antihyperglycemic Medications Demonstrating Cardiovascular Benefit: GLP-1 Receptor Agonists (cont)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rate/100 patient-years</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death, nonfatal MI, nonfatal stroke</td>
<td>3.3</td>
<td>3.9</td>
</tr>
<tr>
<td>CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for UA or HF</td>
<td>5.3</td>
<td>6.0</td>
</tr>
<tr>
<td>All-cause death</td>
<td>2.1</td>
<td>2.7</td>
</tr>
<tr>
<td>CV death</td>
<td>1.2</td>
<td>1.6</td>
</tr>
<tr>
<td>Microvascular event</td>
<td>2.9</td>
<td>3.3</td>
</tr>
<tr>
<td>Major hypoglycemia</td>
<td>1.5</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Source: ACC/AHA 2013 MACE-3 results.

Medications in which two classes have been shown to reduce the risk of cardiovascular events compared to placebo as part of standard care:
1. Sulfonylurea and DPP-4i
2. DPP-4i and SGLT-2i
3. SGLT-2i and GLP-1RA
4. GLP-1RA and meglitinide

Cardiovascular Outcomes Over 30 Months: Canagliflozin vs Other non-SGLT-2 Inhibitors

Heart Failure Hospitalization

Composite CV Endpoints

Canagliflozin + DPP-4i + GLP-1RA vs DPP-4i + GLP-1RA vs GLP-1RA alone vs placebo + DPP-4i vs placebo + GLP-1RA vs placebo + placebo

Source: ACC/AHA 2013 MACE-3 results.
Summary & Implications for Primary Care

- Reducing cardiovascular risk is the key treatment objective for patients with diabetes.
- Available evidence shows that medications from 3 classes do not pose an increased risk of major adverse cardiovascular events.
- Canagliflozin, empagliflozin, liraglutide, semaglutide reduce the risk of key cardiovascular outcomes.

In patients with type 2 diabetes mellitus, the primary treatment goal is to control/reduce:
1. Blood glucose
2. Blood lipid
3. Blood pressure
4. Cardiovascular risk

The goal of cardiovascular safety trials is to demonstrate that the CV safety of the new therapy is:
1. Similar to placebo
2. Similar to metformin
3. Superior to placebo
4. Superior to metformin

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2. DPP-4i and SGLT-2i
3. SGLT-2i and GLP-1RA
4. GLP-1RA and meglitinide

Case Studies in Type 2 Diabetes Mellitus: Focus on Cardiovascular Outcomes Trials

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Volunteer for a follow-up survey and gift card in six weeks.
We need your responses to keep bringing you quality continuing medical education programs.

Case Studies in Type 2 Diabetes Mellitus: Focus on Cardiovascular Outcomes Trials
THANK YOU!
The Role of Non-Statin Therapies for LDL-C Lowering for Management of ASCVD Risk in Family Practice

Disclosures

Michael Cobb, MD, FNLA, has the following relevant financial relationships with commercial interests to disclose:
Consultant - Kowa
Spouses/Beneficiaries: Amgen, AstraZeneca, Kowa, Sanofi

Louis Kunkley, MD, has the following relevant financial relationships with commercial interests to disclose:
Consultant - Amgen

Stephen A. Brunton, MD; Paul P. DiGregorio, MD, FAMEP, and Penny Tenzer, MD, do not have any relevant financial relationships with commercial interests to disclose.

Educational Objectives

This activity is supported by educational funding provided by Amgen.

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Credit

This live activity, Redefining the Role of Non-statin Therapies for LDL-C Lowering; Management of ASCVD Risk in Family Practice, from 11/09/2018 - 11/08/2019, has been reviewed and is acceptable for up to 1.00 Prescribed credits by the American Academy of Family Physicians. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Upon completion of this activity, learners should be able to:
1. SUMMARIZE the latest guidelines and recommendations on cholesterol management from major clinical organizations
2. REVIEW potential cholesterol-lowering therapies beyond statins and explain when these non-statin therapies should be considered
3. STATE the indications in detail for proprotein convertase subtilisin kexin type 9 inhibitor (PCSK9) therapy
Pre-test Question 1
The National Lipid Association (NLA) published recommendations for patient-centered management of dyslipidemia in 2016. These recommendations propose treatment goals for non-HDL-C and LDL-C based on 4 risk categories: Low, Moderate, High, and Very High. Treatment goals for the Low, Moderate, and High risk categories are the same. Which of the following represents the NLA treatment goals for LDL-C?
A. Low, Moderate: High: <70 mg/dL, Very High: <50 mg/dL
B. Low, Moderate: High: <70 mg/dL, Very High: <100 mg/dL
C. Low, Moderate: High: <100 mg/dL, Very High: <150 mg/dL
D. Low, Moderate: High: <100 mg/dL, Very High: <70 mg/dL

Pre-test Question 2
Statin and non-statin combination therapy may improve lipid-lowering efficacy and may improve cardiovascular outcomes. Which of the following combination therapies was studied in the IMPROVE-IT trial and demonstrated reductions in cardiovascular outcomes?
A. Colestipol and simvastatin
B. Ezetimibe and simvastatin
C. Evolocumab and simvastatin
D. Lomitapide and simvastatin

Pre-test Question 3
Which of the following is TRUE regarding indications for PCSK9 inhibitors?
A. Alirocumab is approved for either monotherapy or combination therapy for patients with heterozygous familial hypercholesterolemia (HoFH), homozgyous familial hypercholesterolemia (HoFH), or clinical atherosclerotic cardiovascular disease (ASCVD).
B. Alirocumab is approved for combination therapy with a maximally tolerated statin for patients with HoFH, HoFH, or clinical ASCVD.
C. Evolocumab is indicated to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established CV risk.
D. Evolocumab is just approved for combination therapy for patients with HoFH or clinical ASCVD

Pre-test Question 4
BN is a 37-year-old woman diagnosed at age 13 years with HoFH. Current lipid medications are lovastatin, colestipol, and ezetimibe. BN adheres to a healthy lifestyle with a low-fat diet and regular exercise. However, BN's LDL-C levels remain high with the most recent level of 213 mg/dL. With the HoFH diagnosis, her family history of cardiovascular disease, and the recent increase in LDL-C despite high-dose lipid-lowering drugs, BN asks her physician about the new PCSK9 inhibitors. Which of the following would be an appropriate treatment option for BN?
A. Alirocumab 75 mg subcutaneously monthly (2x/month)
B. Alirocumab 300 mg subcutaneously q4 weeks
C. Evolocumab 300 mg subcutaneously q4 weeks
D. Evolocumab 420 mg subcutaneously q4 weeks

Case Study
- Mark B, a 54-year-old man with familial hypercholesterolemia (FH)
  - BMI: 31.7
  - On treatment LDL-C: <220 mg/dL
  - Smoking: 1 pack/day
  - Typical American diet
  - Exercise: walking >30 minutes, 1 or 2 days/week
  - Medications: atorvastatin 80 mg qd, isosorbide 20 mg qd

What recommendations for the patient?

Cardiovascular Disease and Hyperlipidemia
- Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of morbidity and mortality in the United States
  - Responsible for 1 of 7 deaths
  - Hyperlipidemia is a major ASCVD risk factor
  - Statins are recommended as first-line drug therapy for lowering LDL-C
  - 30% of patients do not achieve lipid-lowering goals, even with maximum statin doses
**Familial Hypercholesterolemia (FH)**
- Inheritance of a pathogenic variant in 1 of the key genes involved in lipoprotein metabolism: APOB, LDLR, or PCSK9
- Heterozygous familial hypercholesterolemia (HeFH)
- Prevalence may be up to 1 in 200 individuals
- Homozygous familial hypercholesterolemia (HoFH)
- Prevalence rate of up to 1 in 300,000 individuals
- Treatment of HeFH or HoFH typically requires additional pharmacotherapy measures and/or LDL apheresis treatments

**FH in Children**
- Early diagnosis and treatment can result in normal life expectancy
- Distinguish FH from non-FH via LDL-C screening in childhood
  - Phaetogenic diagnosis: LDL-C ≥190 mg/dL, or an LDL-C ≥215 mg/dL with family history of premature coronary heart disease and/or high baseline cholesterol in a parent
  - If a parent has a genetic defect, the LDL-C cut-off for the child is ≥150 mg/dL
- Healthy lifestyle and statin treatment (from age 8–10 years) are the foundation of therapy
  - Target LDL-C: <130 mg/dL if <10 years old
  - OR
  - 50% reduction from baseline if ≥10 years old

**How Do I Know When My Patient Has FH?**
**USA: MEDPED Criteria**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Total cholesterol (mg/dL)</th>
<th>LDL-C (mg/dL)</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>220 (155)</td>
<td>170 (130)</td>
<td>96% specificity</td>
</tr>
<tr>
<td>5-10</td>
<td>240 (170)</td>
<td>200 (165)</td>
<td>97% sensitivity</td>
</tr>
<tr>
<td>11-18</td>
<td>270 (200)</td>
<td>230 (205)</td>
<td>98% sensitivity</td>
</tr>
<tr>
<td>18-25</td>
<td>290 (225)</td>
<td>250 (220)</td>
<td>99% specificity</td>
</tr>
</tbody>
</table>

**Lipid Guidelines/Recommendations**

**American Heart Association/American College of Cardiology (AHA/ACC)**
- 2013 Cholesterol Management Guidelines
- 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk
- 2017 Updated Update of 2016 ACC Expert Consensus on the Role of Non-Statin Therapies for Low-density Lipoprotein Cholesterol (LDL-C) Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

**Lipid Guidelines/Recommendations**

**National Lipid Association (NLA)**
- 2015 Dyslipidemia Management Recommendations, Parts 1 and 2
- 2017 Recommendations of the NLA Expert Panel on Treatment with PCSK9
- 2018 Guidelines on the Treatment of High Blood Cholesterol

**2013 AHA/ACC Guidelines and 2016/2017/2018 ACC Updates**
1. Healthy lifestyle habits
2. Appropriate intensity of statin therapy based on ASCVD risk
   - 5 treatment benefit groups
   - Multiple medication therapy in very high risk ASCVD
3. Regularly monitor adherence to lifestyle and drug therapy
4. In cases of statin intolerance, use the maximally tolerated dose of statin (which may be 0)
5. In patients ≥45 years of age being evaluated for primary ASCVD prevention, discuss statin therapy
2018 AHA/ACC Cholesterol Treatment Guidelines

Statin and Non-statin Benefit Groups

Factors to Consider

Optional Interventions to Consider

2018 AHA/ACC: Treatment Benefit Groups

1. Patients ≥ 21 years of age with ASCVD, reduce LDL-C with high-intensity statin therapy or maximally tolerated dose.

2. Patients ≥ 55 years of age with very high risk ASCVD (e.g., LDL-C > 70 mg/dL), to consider adding non-statin to statin therapy.

3. Patients ≥ 75 years of age with severe FH, baseline LDL-C ≥ 160 mg/dL without statin therapy, to consider high-intensity statin therapy.

4. Patients ≥ 45 years of age with diabetes and LDL-C > 70 mg/dL, and moderate-intensity statin therapy or maximally tolerated dose.

5. Patients ≥ 45 years of age without diabetes with LDL-C ≥ 70 mg/dL, with a 10-year ASCVD risk of ≥ 7.5% discuss treatment options, start moderate-intensity statin, if feasible or ≥ 10% risk achieving target LDL-C using maximally tolerated intensity statin.

2018 AHA/ACC: Factors to Consider

- Adherence and lifestyle
- Statin-associated side effects
- Control of other risk factors
- Clinician-patient discussion regarding potential benefits, potential harms, and patient preferences regarding addition of non-statin medications
- Percentage LDL-C reduction (may consider absolute LDL-C level achieved)
- Monitoring of response to therapy, adherence, and lifestyle

2018 ACC: Optional Interventions

- Referral to lipid specialist and registered dietitian or nutritionist
- Ezetimibe
- Bile acid sequestrants
- PCSK9 inhibitors
- Mipomersen, lomitapide, and/or LDL apheresis may be considered by a lipid specialist for patients with FH

Audience Question

Statin-Associated Side Effects

- What are some common causes of statin intolerance?

- Is it feasible and clinically appropriate to use statins in patients with statin intolerance?

Statin-Associated Side Effects

- Along with lifestyle changes, statins are the foundational drug class for treatment of hyperlipidemia
- Adverse effects, particularly myalgia, may limit the application of statins in some populations
- In other patients, statins may not achieve lipid reduction goals
- Alternative therapies may be required to achieve lipid reduction goals

**Statin Intolerance Risk Factors**

**Potential Patient Factors**
- Pre-existing neuromuscular condition, hepatic disease, renal disease, and/or untreated hypothyroidism
- Known history of myopathy or family history of myopathy syndrome
- Certain rare genetic polymorphisms regulating hepatic cytochrome enzyme pathways
- Drug-drug interactions that increase plasma levels of statins

**2015 NLA Dyslipidemia Management Recommendations**
- "Patient-centered"
- Key tenet: lifestyle therapies are central to prevention of ASCVD
  - Nutrition/diet (low in saturated fat)
  - Weight loss
  - Exercise/physical activity

**2015 NLA Dyslipidemia Management Recommendations**
- Lifestyle therapies
- Cholesterol-lowering drug therapies
  - First-line (unless contraindicated): moderate or high-intensity statin
  - Combination therapies

**2015 NLA: Treatment Goals and Criteria for Drug Therapy, Low and Moderate Risks**

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Criteria</th>
<th>Treatment Goal Non-HDL-C, mg/dL</th>
<th>Consider Drug Therapy Non-HDL-C, mg/dL</th>
</tr>
</thead>
</table>
| Low           | • 0 or 1 major ASCVD risk factors (RFs)  
               | • Consider other risk indicators if known | <130                                 | ≥130                                 |
|               |          |                                 | >150                                 | ≥150                                 |
| Moderate      | • 2 major ASCVD RFs  
               | • Consider quantitative risk scoring  
               | • Consider other risk indicators (additional testing may be considered) | <130                                 | ≥130                                 |

**2015 NLA: Treatment Goals and Criteria for Drug Therapy, High-Risk**

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Criteria</th>
<th>Treatment Goal Non-HDL-C, mg/dL</th>
<th>Consider Drug Therapy Non-HDL-C, mg/dL</th>
</tr>
</thead>
</table>
| High          | • ≥5 major ASCVD RFs  
               | • Diabetes (type 1 or 2)  
               | • ≥5 other major ASCVD RFs  
               | • No evidence of end-organ damage  
               | • Chronic kidney disease (CKD) stage 3B  
               | • LDL-C of ≥190 mg/dL  
               | • Quantities not reached in the high-risk threshold | <100                                 | ≥100                                 |

**2015 NLA: Treatment Goals and Criteria for Drug Therapy, Very High-Risk**

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Criteria</th>
<th>Treatment Goal Non-HDL-C, mg/dL</th>
<th>Consider Drug Therapy Non-HDL-C, mg/dL</th>
</tr>
</thead>
</table>
| Very high     | • ASCVD  
               | • Diabetes (type 1 or 2)  
               | • ≥5 other major ASCVD RFs  
               | • Evidence of end-organ damage* | <100                                 | ≥100                                 |

*End-organ damage related to increased arterial/concentric remodeling or plaque burden.**
Non-statin Therapies

**Classes of Drugs**
1. Bile acid binding resins (e.g., colestevisol, colestervam)
2. Cholesterol absorption inhibitor (ezetimibe)
3. PCSK9 inhibitors (alirocumab, evolocumab)

**Additional Drugs for Hypercholesterolemia**
1. Mipomersen: antisense oligonucleotide inhibitor of apolipoprotein B
2. Lomitapide: small molecule inhibitor of microsomal triglyceride transfer protein

**LDL Apheresis**

Bile Acid Binding Resins

**Medications in this class include**:
1. Colesevelam (Colestivas)
2. Cholestyramine (Questran, Questran Light, Cholestipol, Ostyl)
3. Colestevam (Welchol)

**Mechanisms of Action (MOA)**
- Bind bile acids in the GI tract—LDL-C lowering >10%–27%
- Advantages
  - No systemic absorption
- Disadvantages
  - Recent FDA labeling change to remove CV indications
  - Little in the way of convincing outcomes studies for CV risk reduction
- Adverse events
  - Constipation, bloating, nausea, gas

Cholesterol Absorption Inhibitor

- Ezetimibe (Zetia) is the only currently available drug in this class
- Also available in a combination product with Simvastatin
- MOA
  - Inhibition of intestinal cholesterol absorption via the Niemann-Pick C1-Like 1 (NPC1-L1) transmembrane protein (receptor-a230, LDL)
  - May improve CV outcomes in certain patient populations (IMPROVE-IT trial)
- Common adverse events include diarrhea, upper respiratory infection, arthralgia, pain in extremity

Comparison of MOAs:

**Ezetimibe**

**Statins**

Comparison of MOAs:

**Bile Acid Sequestrants**
Comparison of MOAs: PCSK9 Inhibitors

Non-Statin Therapies (con't) REDUCE-IT Trial

Cardiovascular Risk Reduction with Eicosapent Ethyl in High Risk Patients on Statin Therapy

Study Design
- Multicenter, randomized, double-blind, placebo-controlled
- High dose of low-density lipoprotein (LDL) in high-risk patients
- 2 x 800 mg/die of eicosapent ethyl ester (EPA)
- Placebo
- 4,777 patients
- Duration: 7 years (2011-2018)
- Primary Endpoint: Composite of CV death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina
- Age ≥45 with established CVD (Secondary Prevention Cohort) or ≥50 years with diabetes with 51 additional risk factors for CVD (Primary Prevention Cohort)
- Fasting triglyceride ≤500 mg/dL, and <100 mg/dL
- LDL-C ≥200 mg/dL, and ≤100 mg/dL, on stable statin therapy for 12 weeks prior to enrollment

Inclusion Criteria
- Age ≥45 with established CVD (Secondary Prevention Cohort) or ≥50 years with diabetes with 51 additional risk factors for CVD (Primary Prevention Cohort)
- Fasting triglyceride ≤500 mg/dL, and ≤100 mg/dL
- LDL-C ≥200 mg/dL, and ≤100 mg/dL, on stable statin therapy for 12 weeks prior to enrollment

- 4,777 patients

Non-Statin Therapies (con't) REDUCE-IT Trial

Results
- Primary endpoint event occurred
  - Transient ethyl ester: 17.1%
  - Placebo: 22.9%
  - Hazard ratio: 0.77, 95% confidence interval: 0.60 to 0.98, P=0.02
- Effects on Lipids
  - Median change in triglycerides from baseline to 1 year: -14.3% in transient ethyl ester group vs +7.2% in placebo
  - Median change in low-density lipoprotein cholesterol: -11.7% in transient ethyl ester group vs +10.2% in placebo

Case Study
- 54-year-old man with FH
  - BMI: 31.7
  - LDL-C: ≥200 mg/dL
  - Smoking: 1 pack/day
  - High-fat diet
  - Exercise: walking >30 minutes
  - 1 or 2 days/week
  - Meds: atorvastatin 80 mg qd, lisinopril 20 mg qd

What recommendations for the patient?

Audience Discussion Question 2
What medication changes, if any, would you recommend for the patient?
A. Ezetimibe
B. Change statin
C. Fibrate
D. PCSK9i
E. No change

PCSK9 Inhibitors
- A class of lipid-lowering drugs first approved in 2015
- Alirocumab (Praluent), evolocumab (Repatha) are current members of this class
- Monoclonal antibodies (mAbs), a type of biological drug, that require a subcutaneous (SC) route of administration
- Alirocumab is a human mAb of the immunoglobulin G1 (IgG1) isotype
- Evolocumab is a human mAb of the immunoglobulin G2 (IgG2) isotype
PCS93 Inhibitors (MOA): Inactive

PCS93 Inhibitors (MOA): Active PCS93

PCS93 Inhibitors (MOA): Inhibited PCS93

FDA-Approved Indications

Alirocumab
- Adjusted to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or clinical ASCVD who require additional lowering of LDL-C

Evolocumab
- To reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established CVD
- Adjusted to diet, ase, or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe) for treatment of adults with primary hyperlipidemia (including HeFH) to reduce LDL-C
- Adjusted to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL-lowering agents) in patients with HeFH who require additional lowering of LDL-C

Summary of Indication Differences

Alirocumab
- Just as combination therapy with maximally tolerated statin for patients with HeFH or clinical ASCVD
- Not approved for HeFH

Evolocumab
- New, broader indication:
  - To reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established CVD
  - Monotherapy or combination therapy with other lipid-lowering drugs
  - Approved for HeFH as well as HeFH

Alirocumab: Dosing and Administration
- Recommended starting dose: 75 mg SC biweekly (2x/month) or 300 mg q 4 weeks
- Maximum dose: 150 mg SC biweekly
- Available in the following forms:
  - Prefilled, single-dose, disposable pens
  - Syringes in 2 doses/concentrations:
    - 75 mg or 150 mg alirocumab in 1 mL solution
**Evolocumab: Dosing and Administration**

- For patients with HeFH, the recommended dose is 420 mg SC once per month.
- For other patients, including those with HeFH, the recommended dose is either 140 mg biweekly (2x/month) or 420 mg monthly.
- Available in the following forms:
  - Single-use prefilled autoinjector (SureClick) containing 140 mg of evolocumab in 1 mL solution
  - Single-use on-body infuser (PushPortex) for monthly injection with prefilled cartridges containing 420 mg evolocumab in 3.5 mL of solution

**Cardiac Outcomes Studies and Lipid-Lowering Drugs**

**IMPROVE-IT**

- Ezetimibe in combination with simvastatin in patients with recent acute coronary syndrome (ACS)

**FOURIER**

- Evolocumab in patients with established CVD on statin therapy

**ODYSEY OUTCOMES**

- Alirocumab in patients 1–12 months out from an ACS event

**IMPROVE-IT Trial Results**

- Goal: study the safety and efficacy of ezetimibe in combination with simvastatin compared with simvastatin alone in reducing CV events in patients at high risk
- Multicenter, randomized, double-blind, active-control trial
- Patients randomized to receive ezetimibe 10 mg/simvastatin 40 mg (n=5087) or placebo/simvastatin 40 mg (n=6077)
- Patients were followed for 6 years

**FOURIER Trial Results**

- Goal: evaluate the efficacy and safety of evolocumab, a PCSK9 inhibitor, among subjects with elevated CV risk on statin therapy
- Randomized, parallel, double-blind, placebo-controlled trial
- Patients assigned to evolocumab 140 mg SC q2 weeks or 420 mg monthly (n=13,764) versus placebo q2 weeks (n=13,760)

**IMPROVE-IT Trial Results**

- Ezetimibe/simvastatin reduced LDL-C compared with placebo/simvastatin: 53.7 mg/dL versus 69.5 mg/dL (P<0.001)
- Ezetimibe/simvastatin compared with placebo/simvastatin significantly reduced the risk of:
  - Primary end point (CV death/MI/thrombolytic use): 32.7% versus 34.7% (HR: 0.94, 95% CI: 0.86-0.99, P=0.016)
  - MI: 13.1% versus 14.8% (P<0.002)
  - Stroke: 4.2% versus 4.8% (P=0.05)
  - CV death/stroke: 20.4% versus 22.2% (P=0.003)

**FOURIER Trial Results**

- Evolocumab reduced LDL-C by up to 59% compared with placebo (P<0.001)
- Evolocumab, compared with placebo, significantly reduced the risk of:
  - Primary end point (composite of CV death, MI, stroke, hospitalization for UA, or coronary revascularization): 9.8% versus 11.3% (HR: 0.85, 95% CI: 0.79-0.92, P<0.001)
  - Key secondary end point (composite of CV death, MI, or stroke): 5.9% versus 7.4% (HR: 0.90, 95% CI: 0.73-0.98, P<0.001)
**FOURIER Trial: Prior MI Subset**

- In the FOURIER Trial, 22,361 patients had prior MI
  - MI within 2 years prior: 8402 patients (39%)
  - Multiple MIs (≥2): 5285 patients (24%)
  - Residual, multivessel CAD: 5618 patients (25%)
  - Evolocumab lowered LDL-C and reduced the risk of CV death, MI, stroke, hospitalization for UA, or coronary revascularization in high-risk patients

**Preliminary ODYSSEY Outcomes Topline Results**

- Data presented at the American College of Cardiology 2018 Meeting
- Random, placebo-controlled trial with nearly 19,000 patients
- No safety signal with alirocumab other than injection-site reactions (with treatment extending >3 years in some patients)

**PCSK9 Inhibitors: Adverse Events**

- Both alirocumab and evolocumab are generally well tolerated
- Adverse events are typically limited to nasopharyngitis, injection-site reactions, arthralgia, myalgia, and headache
- Concerns about the impact of lowering LDL-C levels have been mitigated based on subanalyses of FOURIER trial results
  - LDL-C levels were reduced to <7 mg/dL in some patients
  - No safety concerns observed over the 22-year study period

**Therapy Recommendations**

- Several professional organizations and associations have updated existing guidelines and recommendations based on the efficacy and safety of PCSK9 inhibitors
  - National Lipid Association
  - American College of Cardiology
  - American Association of Clinical Endocrinologists/American College of Endocrinology

**FOURIER Trial: Prior MI Subset**

<table>
<thead>
<tr>
<th>Patient Subset (number of patients)</th>
<th>Relative Risk Reduction, Primary Endpoint</th>
<th>Hazard Ratio (range)</th>
<th>Absolute Risk Reduction at 3 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI within 2 years prior (8402)</td>
<td>20% (0.80)</td>
<td>82% (0.72-0.93)</td>
<td>3.4%</td>
</tr>
<tr>
<td>≥2 MIs (5285)</td>
<td>18% (0.82)</td>
<td>82% (0.72-0.93)</td>
<td>3.4%</td>
</tr>
<tr>
<td>Residual, multivessel CAD (5618)</td>
<td>23% (0.79)</td>
<td>82% (0.69-0.93)</td>
<td>3.6%</td>
</tr>
</tbody>
</table>


2017 NLA Expert Panel Recommendations on PCSK9 Inhibitors

Recommendations for 3 patient populations:
1. ASCVD
2. LDL-C ≥190 mg/dL (including polygenic hypercholesterolemia, HeFH, and HoFH phenotype)
3. Very high-risk/statin intolerance

2017 NLA Recommendations on PCSK9 Inhibitors

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>LDL-C Criteria</th>
<th>Strength/Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCVD</td>
<td>≥190 mg/dL</td>
<td>AHigh</td>
</tr>
<tr>
<td>Progressive ASCVD</td>
<td>≥190 mg/dL</td>
<td>BModerate</td>
</tr>
<tr>
<td>LDL-C ≥190, age 40-79 years</td>
<td>≥150 / ≥190</td>
<td>BBModerate</td>
</tr>
<tr>
<td>LDL-C ≥190, age 40-79 years</td>
<td>&lt;150 / &lt;190</td>
<td>BModerate</td>
</tr>
<tr>
<td>Uncontrolled risk markers, age 40-79 years</td>
<td>≥120 / ≥190</td>
<td>BLModerate</td>
</tr>
<tr>
<td>Uncontrolled risk markers, age 19-39 years</td>
<td>≥120 / ≥190</td>
<td>BLModerate</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>≥190 mg/dL</td>
<td>CLow</td>
</tr>
<tr>
<td>ARVD</td>
<td>≥190 mg/dL</td>
<td>Clinical judgment</td>
</tr>
</tbody>
</table>

Potential Barriers to PCSK9 Inhibitor Access

- NLA survey reported initial denial rates of >65%
- Approval rates were higher for patients with heart failure (42%) compared with ASCVD (36%)
- Documentation reported to be the most critical factor in facilitating approvals

(N.B.—Study was conducted prior to new indication for evolocumab)

Additional Potential Barriers to Access

- Approaches used by payers to manage access to costly medications
  - Prior authorization
  - Step therapy
  - Also referred to as "fail first" therapy
- Burdensome appeals process
- Formulary restrictions

Prior Authorization Template

- 3 sections
  - Prescriber information
  - Patient history
  - Current therapy
**Prior Authorization Template**

**PCSK9 Inhibitor Prior Authorization Form**

To be completed by Prescriber

<table>
<thead>
<tr>
<th>Prescriber Information</th>
<th>Patient Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescriber’s Name:</td>
<td>Patient’s Medical ID:</td>
</tr>
<tr>
<td>Phone #:</td>
<td>Phone #:</td>
</tr>
<tr>
<td>Fax #:</td>
<td>Fax #:</td>
</tr>
</tbody>
</table>

Prescription Information

Drug Requested: 
- New therapy
- Continuation

Frequency of Dosing: 
- Quantity Requested:

**Prior Authorization Template**

Which Non-statin to Use?

- Primary goal: LDL reduction for patients at the highest risk
- Use recommendations from guidelines as applicable for patient
- Patient status, particularly if there are risks for ASCVD
- Emphasize adherence to lifestyle recommendations and to prescribed therapy
- Coordinate with other health care professionals
- Discuss economic issues with patients
  - If cost is a major factor, it will affect compliance/adherence
  - When available, use manufacturer financial assistance programs

**Case Study**

- 54-year-old man with FH
  - BMI: 31.7
  - New LDL-C: <195 mg/dL
  - Smoking down to 0.5 pack/day
  - Diet modifications made
  - Exercise: walking >30 minutes, 3 or 4 days/week
  - Meds: atorvastatin 80 mg qd, lisinopril 20 mg qd, ezetimibe

What recommendations for the patient?

**Summary**

- Statin therapy is not feasible for every patient
- Clinical guidelines provide direction on the use of non-statin, including ezetimibe and PCSK9 inhibitors
- Obtaining payer approval for a PCSK9 inhibitor will require coordination of the health care team and clear documentation for payer processes
- Preliminary clinical trial data for alirocumab may result in updated indications
Additional Resources

- National Lipid Association (www.lipid.org)
- Resources for patients and clinicians
- The FH Foundation (leifhfoundation.org)
- Resources for patients and clinicians

Post-test Question 1

The National Lipid Association (NLA) published recommendations for patient-centered management of dyslipidemia in 2016. Those recommendations propose treatment goals for non-HDL-C and LDL-C based on 4 risk categories: Low, Moderate, High, and Very High. Treatment goals for the Low, Moderate, and High risk categories are the same. Which of the following represents the NLA treatment goals for LDL-C?
A. Low, Moderate, High: <70 mg/dL, Very High: <70 mg/dL
B. Low, Moderate, High: <70 mg/dL, Very High: <100 mg/dL
C. Low, Moderate, High: <100 mg/dL, Very High: <100 mg/dL
D. Low, Moderate, High: <100 mg/dL, Very High: <70 mg/dL

Post-test Question 2

Statin and nonstatin combination therapy may improve lipid-lowering efficacy and may improve cardiovascular outcomes. Which of the following combination therapies was studied in the IMPROVE-IT trial and demonstrated reductions in cardiovascular outcomes?
A. Colesevelam and simvastatin
B. Ezetimibe and simvastatin
C. Evolocumab and simvastatin
D. Lomitapide and simvastatin

Post-test Question 3

Which of the following is TRUE regarding indications for PCSK9 inhibitors?
A. Alirocumab is approved for either monotherapy or combination therapy for patients with heterozygous familial hypercholesterolemia (HeFH), homozygous familial hypercholesterolemia (HoFH), or clinical atherosclerotic cardiovascular disease (ASCVD).
B. Alirocumab is approved for combination therapy with a maximally tolerated statin for patients with HeFH, HoFH, or clinical ASCVD.
C. Evolocumab is indicated to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established CVD.
D. Evolocumab is just approved for combination therapy for patients with HeFH or clinical ASCVD.

Post-test Question 4

BN is a 27-year-old woman diagnosed at age 13 years with HeFH. Current lipid medications are lovastatin, colesevelam, and ezetimibe. BN adheres to a healthy lifestyle with a low-fat diet and regular exercise. However, BN’s LDL-C levels remain high with the most recent level of 215 mg/dL. With the HoFH diagnosis, her family history of cardiovascular disease, and the recent increase in LDL-C despite high-dose lipid-lowering drugs, BN asks her physician about the new PCSK9 inhibitors. Which of the following would be an appropriate treatment option for BN?
A. Alirocumab 75 mg subcutaneously biweekly (Zoluxome)
B. Alirocumab 300 mg subcutaneously q4 weeks
C. Evolocumab 300 mg subcutaneously q4 weeks
D. Evolocumab 420 mg subcutaneously q4 weeks

Q&A
Thank you for your attention and participation!
Notes........
Examining the Role of Family Physicians in the Early Recognition and Management of Chronic Heart Failure

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Disclosures
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Heart Failure in America
- More than 5 million Americans are diagnosed with HF each year.
- Nearly 100,000 new patients are diagnosed every hour.
- The US spends $1 billion every year on HF.
- 1 million hospitalizations each year.
- HF is the #1 cause of hospitalization for patients aged 65 years and older.
- Hospitalizations account for 80% of all money spent on HF.
- The risk of death is increased after a hospitalization for HF.
- Up to 50% of patients die within 5 years of a diagnosis of HF.

Initial Evaluation and Diagnosis of the Heart Failure Patient

Natural History of Chronic and Acute Heart Failure

Primary Care Physician Diagnosis
Rich, Aged 70 Years With a History of Hypertension:

- Laboratory results: Cr:1.5, K:4.8
- Current medications: Lisinopril 10 mg once daily

Would you evaluate this patient for heart failure?
Is noninvasive imaging appropriate for initial evaluation of heart failure?

Definitions of HFpEF and HFpEF¹

<table>
<thead>
<tr>
<th>Classification</th>
<th>Functional Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. HF with</td>
<td>D = Dyspnea</td>
<td>Also referred to as clinical HF</td>
</tr>
<tr>
<td>reduced ejection fraction (HFrEF)</td>
<td>D = Dyspnea</td>
<td>Randomized controlled trials have mainly enrolled patients with HFrEF</td>
</tr>
<tr>
<td>2. HF with preserved ejection fraction (HFpEF)</td>
<td>= 50%</td>
<td>Also referred to as diastolic HF</td>
</tr>
<tr>
<td>a. HFpEF, borderline</td>
<td>40%</td>
<td>Several different criteria have been used to further define HFpEF</td>
</tr>
<tr>
<td>b. HFpEF, increased</td>
<td>&gt; 40%</td>
<td>Diagnosis of HFpEF is challenging because it is largely one of excluding other potential noncardiac causes of symptoms suggestive of HF</td>
</tr>
</tbody>
</table>

HF: Heart Failure
HFrEF: Heart Failure with Reduced Ejection Fraction
HFpEF: Heart Failure with Preserved Ejection Fraction

Classification of HF: ACCF/AHA Stages of HF¹

A. High risk for HF but without structural heart disease or symptoms of HF
B. Structural heart disease but without signs or symptoms of HF
C. Structural heart disease with prior or current symptoms of HF
D. Refractory HF requiring specialized interventions

Classification of HF: NYHA Functional Classification¹

I. No limitation of physical activity
   - Slight limitation of physical activity
II. Comfortable at rest
   - Ordinary physical activity results in symptoms of HF
III. Marked limitation of physical activity
   - Comfortable at rest
   - Less-than-ordinary activity causes symptoms of HF
IV. Unable to carry on any physical activity without symptoms of HF

NYHA: New York Heart Association

Initial Workup of Newly Diagnosed HF¹

- History, exam, electrocardiogram
- Echocardiogram
- Laboratory testing
- Assessment of functional capacity
- Assessment for CAD in patients at risk

In All Cases
- Cardiac catheterization
- Cardiac MRI
- Endomyocardial biopsy
- Genetic testing

In Selected Cases

Diagnosing Heart Failure: Diagnostic Tests

- Serum BNP in the acute setting can help hone the diagnosis of HF
- Serum BNP serial monitoring has not been definitively found to be clinically useful in monitoring the stable patient
**BNP for HF Diagnosis**

Patients Presenting to ER With Dyspnea

![Image of BNP levels and NYHA classes](PeerView.com)

**Common Electrocardiogram Findings**

- Electrocardiogram findings of:
  - LV hypertrophy
  - Left bundle branch block
  - Intraventricular conduction delay
  - Nonspecific ST-segment and T wave changes
  - Q waves in contiguous leads strongly implicate a previous myocardial infarction and coronary artery disease as the cause

![Image of electrocardiogram findings](PeerView.com)

**2017 Guidelines Biomarkers Indications for Use**

- ACC/AHA/HFSA-17
- ACC/AHA/HFSA-18
- ACC/AHA/HFSA-19
- ACC/AHA/ESC-2013
- ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure
- Corresponding author: PeerView.com

**Rich, Aged 70 Years With a History of Hypertension**

- Presents with shortness of breath, coughing at night, edema in lower extremities
- Exam: Upright BP 135/85 mmHg, heart rate 68 bpm
- Laboratory results: Hgb 15.5 Kt/dL, inr 3.5, albumin 3.0 g/dL
- Current medications: Lisinopril 10 mg once daily, atenolol 50 mg twice daily, spironolactone 25 mg once daily
- Is noninvasive imaging appropriate for initial evaluation of heart failure?

![Image of patient history](PeerView.com)

**Improving Heart Failure Management and Coordinating Care Throughout the Disease Continuum**

![Image of heart failure management](PeerView.com)

**Pathophysiology of HF With Reduced EF**

- Cardiomyopathy
- Cardiac overload
- Coronal disease
- Left ventricular dysfunction
- Neurohumoral activation
- 1. Peripheral organ blood flow
- 2. Renal blood flow
- 3. Renal sodium retention
- LV diastolic dysfunction
- LV hypertrophy
- Symptoms, fluid retention, death

![Image of pathophysiology](PeerView.com)
Neurohormonal Balance in HF With Reduced EF

<table>
<thead>
<tr>
<th>RAAS activation</th>
<th>Compensatory mediators</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Angiotensin II</td>
<td>• Nitric oxide</td>
</tr>
<tr>
<td>• Aldosterone</td>
<td>• Prostaglandins</td>
</tr>
<tr>
<td>• Norepinephrine</td>
<td>• Bradykinin</td>
</tr>
<tr>
<td>Vasopressin</td>
<td></td>
</tr>
<tr>
<td>Endothelin</td>
<td></td>
</tr>
</tbody>
</table>

RAAS, renin-angiotensin-aldosterone system

Vasodilation
Fluid retention
Fibrosis
Hypertrophy

Nepriylin as a Therapeutic Target

- Nepriylin is responsible for the breakdown of a number of endogenous vasoactive peptides, including the natriuretic peptides
- Inhibition of nepriylin potentiates the action of these peptides
- Because angiotensin II is also a substrate for nepriylin, nepriylin inhibitors must be coadministered with a RAAS blocker
- The combination of a nepriylin inhibitor and an ACEI is associated with unacceptably high rates of angioedema

PARADIGM-HF: CV Death or HF Hospitalization (Primary Endpoint)

- Eplerenone (n = 4,212)
- Sacubitril/Valsartan (n = 4,187)

Cardiovascular
Death
Hospitalization

Overall Mortality
HF Death
Sudden Death

PARADIGM-HF: Other Key Endpoints

- Sacubitril/Valsartan: Greater Mortality Reduction Than With ACEI/ARB

PARADIGM-HF: Summary of Findings

- Sacubitril/Valsartan was more effective than eplerenone
  - Reducing the risk of CV death and HF hospitalization
  - Reducing the risk of CV death by incremental 20%
  - Reducing the risk of HF hospitalization by incremental 21%
  - Reducing all-cause mortality by incremental 10%
  - Incrementally improving symptoms and physical limitations
- Sacubitril/Valsartan was better tolerated than enalapril
  - Less likely to cause cough, hyperkalemia, or renal impairment
  - Less likely to be discontinued because of an adverse event
  - More hypotension, but no increase in discontinuations
  - Not more likely to cause serious angioedema

In heart failure with reduced ejection fraction, when compared with recommended doses of enalapril.
**PARADIGM-HF: Adverse Events**

<table>
<thead>
<tr>
<th>Event</th>
<th>Sacubitril/ Valsartan</th>
<th>Enalapril</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximately identified adverse events, % (n=1,177)</td>
<td>14.0</td>
<td>9.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Symptomatic hyperkalemia</td>
<td>4.3</td>
<td>5.6</td>
<td>.007</td>
</tr>
<tr>
<td>Serum creatinine ≥5 mg/dl</td>
<td>3.3</td>
<td>4.5</td>
<td>.007</td>
</tr>
<tr>
<td>Cough</td>
<td>11.3</td>
<td>14.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Discontinuation for adverse event</td>
<td>10.7</td>
<td>12.2</td>
<td>.02</td>
</tr>
<tr>
<td>Discontinuation for hypotension</td>
<td>0.8</td>
<td>0.7</td>
<td>NS</td>
</tr>
<tr>
<td>Discontinuation for hyperkalemia</td>
<td>0.2</td>
<td>0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Discontinuation for renal impairment</td>
<td>0.7</td>
<td>1.4</td>
<td>.011</td>
</tr>
</tbody>
</table>

Angioedema ( adjudicated)
- Medications; no hospitalization: 0.2 vs 0.2 NS
- Hospitalized; no airway compromise: 0.1 vs 0.1 NS
- Airway compromise: 0 vs 0 NS

**Influence of Sacubitril/Valsartan on 30-Day Readmission**

![Graph showing influence of Sacubitril/Valsartan on 30-Day Readmission](image1)

**Effect of Sacubitril/Valsartan on BNP and NT-proBNP Levels**

![Graph showing effect of Sacubitril/Valsartan on BNP and NT-proBNP Levels](image2)

**Improvement in QOL With Sacubitril/Valsartan: Secondary Analysis of the PARADIGM-HF Trial**

![Graph showing improvement in QOL with Sacubitril/Valsartan](image3)

**2017 ACC/AHA/HFSA Focused Update of the 2013 ACC/AHA Guideline for the Management of Heart Failure**

- **ACEI or ARB or ARNI** in patients with chronic heart failure NYHA class II or III who tolerate and ACEI or ARB, replaced by an ARNI is recommended to further reduce morbidity and mortality.

---

The Funny Current (If) and Ivabradine

Impact of Heart Rate on Outcomes in HF

SHIFT Trial Primary Composite Endpoint: CV Death or Hospital Admission for Worsening HF

Ivabradine Treatment Discontinuation

2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

Optimization of Ivabradine

- Starting dose is 5 mg twice daily
- Target heart rate is 50-60 bpm
Rich, 70-Year-Old Man With HFrEF

Laboratory results:
- Cr 1.5 x 4.0
- NT-proBNP 1.058 pg/ml

Current medications:
- Lisinopril 10 mg once daily
- Coreg 12.5 mg once daily
- Spironolactone 25 mg once daily

- Switch from lisinopril to enalapril/vasopressin
- Start ACEI for 36 hours before switching/vasopressin
- Start with enalapril/vasopressin 1/2 mg once daily
- Double the dose after 2 to 4 weeks as tolerated and maintain dose of 20/30 mg once daily

Serial Elevation and Titration of Medications

Endotracheal intubation/sedation

Endotracheal intubation/sedation

Stabilization

Assess response to therapy and consider repositioning

Endotracheal intubation/sedation

Stabilization

Triggers for HF Patient Referral to a Specialist/Program

1. New sheet HR, regardless of EF, severe LV systolic dysfunction; NSR or diastolic dysfunction; or mild LV systolic dysfunction; or moderate diastolic dysfunction; or severe diastolic dysfunction

2. Clinical HF with high risk features, high risk development of LV systolic dysfunction

3. To optimize with management of LVOT; including replacement of ACEI or ARB therapy with AKI for slightly elevated, at-risk cardiovascular risk factors; twice daily therapy; increased risk for complications

4. Persistent diastolic dysfunction, systolic dysfunction >35%, severe LV systolic dysfunction >50%

5. Generalized HF therapy strategy, at risk

6. Annual review of patients with hospitalization for HF with new onset or worsening of HF, exacerbation of medical conditions, and changes in treatment regimens, life style, and mental health

7. Assess the possibility of participation in a clinical trial

Managing Lack of Response to HF Therapy/Instability

Remember this acronym to assist in decision-making for referral to advanced HF specialist

I-NEED-HELP

I = IV inotropes
N = NYHA III/IV or persistently elevated natriuretic peptides
E = End-organ dysfunction
D = Ejection fraction <35%
E = Diuretic overload
D = Defibrillator shocks
H = Hospitalizations >1
E = Edema despite escalating diuretics
L = Low blood pressure, high heart rate
P = Prognostic medication—progressive intolerance or down-titration of GDMT

HFpEF: ACCF/AHA Guidelines

Class I
- Control hypertension
- Chronic medical conditions
- Judicious use of diuretics

Class IIa
- Risk factor modification
- Management of AF
- β-blockers, ACEI, ARB, for post-myocardial infarction
- Contraindicated ARBs to reduce hospitalization

Class IIc
- Use of β-blockers, ACEI, ARB, for post-myocardial infarction
- Management of AF according to published clinical practice guidelines
- Use of β-blockers, ACEI, ARB, for post-myocardial infarction
- Use of β-blockers, ACEI, ARB, for post-myocardial infarction
- Use of β-blockers, ACEI, ARB, for post-myocardial infarction
- Management of AF according to published clinical practice guidelines

Rich, 70-Year-Old Man With HFrEF

Current medications:
- Carvedilol 2.5 mg twice daily
- Spironolactone 25 mg once daily

Switched from lisinopril to enalapril/vasopressin

- Which methods should we use to encourage self-monitoring care, ensure adherence to treatment, and improve patient outcomes?
Characteristics and Components of HF Management Programs

**Components of HF Management**

- Optimized medical and device management
- Adequate patient education, with special emphasis on adherence and self-care
- Patient involvement in symptom monitoring and flexible dosing use
- Follow-up after discharge (regular clinic and home-based visits, possibly telephone support or nurse triad visits)
- Increased access to healthcare (through in-person follow-up and by telephone contact, possibly through remote monitoring)
- Facilitated access to care during episodes of decompensation
- Assessment of (and appropriate intervention in response to) an unexplained change in weight, functional status, fluid status, or laboratory findings
- Access to advanced treatment options
- Provision of psychosocial support to patients and family/donor caregivers

**Multidisciplinary Framework to Optimize Health Outcomes in HF and Multimorbidity (ARISE-HF)**

- **A** Acknowledge multimorbidity as a clinical syndrome that is associated with poor health outcomes
- **R** Routinely profile all patients hospitalized with HF to determine the extent of concurrent multimorbidity (using a standardized protocol, adapted to the local healthcare system)
- **I** Identify individualized priorities and person-centered goals based on the extent and nature of multimorbidity
- **S** Support individualized, home-based, multidisciplinary, case management to supplement standard HF management
- **E** Evaluate health outcomes well beyond acute hospitalization and encompass all-cause events

Monitoring Patients With Heart Failure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Requires Face-to-Face Encounter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms (PND, orthopnea, etc)</td>
<td>✓</td>
</tr>
<tr>
<td>Jugular venous pressure</td>
<td>✓</td>
</tr>
<tr>
<td>Hepatomegaly reflex</td>
<td>✓</td>
</tr>
<tr>
<td>S3</td>
<td>✓</td>
</tr>
<tr>
<td>Raies</td>
<td>✓</td>
</tr>
<tr>
<td>Daily weight</td>
<td>✓</td>
</tr>
<tr>
<td>BNP</td>
<td></td>
</tr>
<tr>
<td>Intra-thoracic impedance</td>
<td></td>
</tr>
<tr>
<td>Heart rate variability</td>
<td>✓</td>
</tr>
</tbody>
</table>

Requirements for Self-Care

**Adherence to Treatment**
- Medications
- Diet
- Follow-up

**Preventative Behaviors**
- Exercise
- Weight loss
- Alcohol and smoking cessation
- Caution with nonprescription medications

Other Self-Care Recommendations

- Fluid restriction (1.5-2.0 L/d) only for those with refractory symptoms and hypotension
- Moderation of alcohol intake
  - Abstinence recommended for those with alcoholic cardiomyopathy
- Smoking cessation
- Influenza/pneumonia vaccination
- Avoidance of NSAIDs, herbal medications
- Exercise

Adherence to Sodium Restriction Is Poor

- Estimated usual intake of sodium among US adults aged 18-99 years
- 50% of patients (N = 2,371) discharged from hospital recalled dietary advice about sodium restriction
- 38% reported following the advice

EuroHeart Failure Survey

- Higher intake associated with increased risk of cardiovascular disease
- Lower intake associated with decreased risk of cardiovascular disease
Challenges in Adhering to a Low-Sodium Diet

- Lack of knowledge of sodium content of foods
- Inability to read food labels
- Reliance on prepared foods
- Multiple dietary restrictions
  - Two-thirds of patients trying to follow 2 or more diets
- Cost/availability of low-sodium alternatives
- Lack of culturally relevant dietary guidance

A consultation with a nutritionist may help

The Role of the PCP in HF Care

You are the captain of the ship!

- Prevention
- Diagnosis
- Management of comorbidities
- Advanced care planning
- Central role in care transition
- Gatekeeper for referrals

Please remember to complete and submit your Post-Test and Evaluation for CME credit.

Missed anything?

Visit us at: www.peerview.com/HeartFailure
- Download slides and Practice Aids
- Watch the online version of this activity
- Join the conversation on Twitter @PeerView

Thank you and have a good day.
Antibiotic Stewardship: Optimizing Antibiotic Use and Patient Outcomes
11:15 AM – 11:45 AM  Core Elements of Antibiotic Stewardship; Sarah Kabbani, MD; Medical Officer at the Center for Disease Control and Prevention, Atlanta, GA
11:45 AM-12:15 PM  West Virginia Updates - Projects and Success (this will include the Samantha Mullins APRN, MSN, FNP-C with Bureau for Public Health- Division of Infectious Disease Epidemiology; Deborah Ann Fosson, RN, BSN, Project Manager with Quality Insignts; Valerie Jividen, MSN, MHA; with West Hospital Association)

Program continues after lunch........

1:00pm-1:45pm  Outpatient Antibiotic Stewardship; Joseph Evans, MD; Marshall Pediatrics, Huntington, WV
1:45pm-2:15pm  Antibiotic Stewardship in the Long Term Care Setting; Anita Lorenza, PharmD, BCGP; Director Clinical Pharmacy Services, Stonerise Healthcare, So. Charleston, WV
2:15pm-2:45pm  Optimizing Antibiotic Prescribing in the Outpatient Setting; Sarah Kabbani, MD, MSc; Public Health, Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases, Dept. of Healthcare Quality Promotion, Prevention Response Branch, Office of Antibiotic Stewardship; Atlanta, GA
2:45-3:00pm Questions/Answer Session
Knowledge, Attitudes, and Beliefs: West Virginia Prescriber Survey

Objectives
- Define outpatient antibiotic prescribing rates in West Virginia
- Define methods used in prescriber survey
- Discuss results of prescriber survey
- Discuss actions/interventions taken in West Virginia to address antimicrobial resistance

Background of Problem
- Antibiotic resistance has become a worldwide concern
- Classified as one of the top five health threats
- Studies indicate that 30-50% of antibiotics prescribed are unnecessary or inappropriate
- The national average for prescribing antibiotics is 838 per 1,000 population
- West Virginia has 1,319 per 1,000 population

Survey Background
- Prescribing Practices of West Virginia Healthcare Providers
- Method: Mail in survey
- Target: Physicians, nurse practitioners, and physician assistants
- Date: Began May 2016
- Total number prescribers: 7,539
- Total number prescribers eligible: 5,235 (69.4%)
- Total responded: 805 (15.3%)
- The survey consisted of 37 questions

Survey Results

Where did you attend medical school?

Survey Results (cont’d)

Years in Practice?

What setting(s) do you currently practice in?
Summary

- Prescribers perceive patients and/or caregivers as insisting on receiving an antibiotic
- Antibiotic overuse is believed to contribute to antimicrobial resistance
- Prescribers believe antibiotic resistance and overprescribing is a problem in West Virginia

West Virginia in Action

- Prescriber Survey
- Onsite education and training
- Data analysis
- Partner collaborations and initiatives
- Antibiotic stewardship programs
- Provided resource discs to over 800 prescribers
- Participated in a "back pack" project
- Clinical practice guidelines

West Virginia in Action (cont'd)

- Needs assessments for urgent cares and emergency departments
- Partnered with the Infection Control Assessment and Response project
- Presentations at state and national conferences
- Proclamation declaring State Antibiotics Awareness Week
- Participated in grand rounds
- National Long Term Care Antibiotic Playbook
- Training for new infection control practitioners

Contact Information

Samantha Mullins APRN, MSN, FNP-C
Antibiotic Stewardship Coordinator
West Virginia Department of Health and Human Resources
Bureau for Public Health
Office of Epidemiology and Prevention Services
Division of Infectious Disease Epidemiology
350 Capitol St., Rm. 125
Charleston, WV 25301
Phone: (304) 556-4046 (Direct)  
(304) 558-5358, Ext. 1 (Main)
Fax: (304) 558-6335
Email: Samantha.L.Mullins2@wv.gov
Outpatient Antibiotic Stewardship:
Project Details
Debby Fossen
Quality Insights Project Coordinator

Objectives
- Attendees will be able to identify the 4 outpatient core elements of the outpatient antibiotic stewardship program
- Attendees will be able to identify one key action to implement for each core element

Core Elements for Outpatient Antibiotic Stewardship
- The CDC Core Elements for Outpatient Antibiotic Stewardship were released in November 2016
- Completion of at least one key action is required for each of the four core elements

1st Core Element: Commitment
- Can your facility demonstrate dedication to and accountability for optimizing antibiotic prescribing and patient safety related to antibiotics?
- If yes, indicate which of the following are in place. (Select all that apply.)
  - Write and display public commitments in support of antibiotic stewardship.
  - Identify a single leader to direct antibiotic stewardship activities within a facility.
  - Include antibiotic stewardship-related duties in position descriptions or job evaluation criteria.
  - Communicate with all clinic staff to set patient expectations.

2nd Core Element: Action
- Has your facility implemented at least one policy or practice to improve antibiotic prescribing?
- If yes, indicate which interventions are in place. (Select all that apply.)
  - Use evidence-based diagnostic criteria and treatment recommendations.
  - Use delayed prescribing practices or watchful waiting, when appropriate.
  - Provide communications skills training for clinicians.
  - Require explicit written justification in the medical record for non-recommended antibiotic prescribing.
  - Provide support for clinical decisions.
  - Use call centers, nurse hotlines, or pharmacist consultations as triage systems to prevent unnecessary visits.
3rd Core Element: Tracking and Reporting

- Does your facility monitor at least one aspect of antibiotic prescribing?
  - Self-evaluate antibiotic prescribing practices. (This intervention only applies to solo practitioners or practices with fewer than 5 clinicians as long as all clinicians participate.)
  - Participate in continuing medical education and quality improvement activities to track and improve antibiotic prescribing. (This intervention only applies if all clinicians in the practice participate in the activity.)
  - Track and report antibiotic prescribing for one or more high priority conditions.
  - Track and report the percentage of all visits leading to antibiotic prescriptions.
  - If already tracking and reporting one of the above, track and report at the level of a health care system, complications of antibiotic use & antibiotic resistance trends among common outpatient bacterial pathogens.
  - Assess and share performance on quality measures and established reduction goals addressing appropriate antibiotic prescribing from health care plans and plans.

4th Core Element: Education and Expertise

- Does your facility provide resources to clinicians and patients on evidence-based antibiotic prescribing?
  - If yes, indicate how your facility provides antibiotic stewardship education to patients. (Select all that apply.)
    - Use effective communication strategies to educate patients about when antibiotics are and are not needed.
    - Educate about the potential harms of antibiotic treatment.
    - Provide patient education materials.
  - If yes, indicate how your facility provides antibiotic stewardship education to clinicians. (Select all that apply.)
    - Provide face-to-face educational training (academic detailing).
    - Provide continuing education activities for clinicians.
    - Ensure timely access to persons with expertise.

Benefits of Participation

- All education, technical assistance, and tools/resources are free.
- Receive education on the fundamentals of outpatient antibiotic stewardship and implementing in the outpatient setting.
- Education on Core Elements.
- Receive education to educate patients and caregivers on antibiotic stewardship.
- Network with experts in WV and the country working on antibiotic stewardship.
- Be a member of a five-state LAN and participate in best practice activities on antibiotic stewardship.

Expectations of Participation

- Complete the participation agreement form required by CMS.
- Agree to participate through July 2019.
- Agree to publicly disclose participation.
- Form an interdisciplinary team to implement the Core Elements.
- Identify a team champion and a day-to-day leader.
- Participate in LAN events, educational sessions, webinars, and conference calls.
- Share results, best practices, and lessons learned.

Thank you.
We look forward to working with you.
West Virginia Hospital Association’s Antibiotic Stewardship Program

Valerie Jividen, MSN, MHA, RN
Quality Improvement Manager

Objectives:
• Describe the rationale and goals of the Antibiotic Stewardship Collaborative (ASC)
• Discuss the elements of the ASC
• Analyze the results of the ASC
• Review sustainment of successes

• “...resistance to antibiotics has become a major threat to public health.”- World Health Organization
• “Dangerous infections that are resistant to antibiotics are spreading and growing stronger, with dire consequences”. - Consumer Reports
• “We can either work to improve antibiotic use and prevent infections, or watch as the clock turns back to a world where simple infections kill people”. – Tom Frieden, CDC, Wall Street Journal

Antibiotic prescribing in Hospitals Often:
• Inconsistent
• Inappropriate
• Contributes to Antibiotic Resistance

The CDC Recommended Core Elements:
• Leadership Commitment
• Accountability
• Drug Expertise
• Active Oversight
• Tracking
• Reporting
• Ongoing Education

KMA Collaboration:
• 24/7 Access and Support of Infectious Disease Physician and Team
• Train and Empower Physician and Pharmacy Champions
• Concurrent Monitoring of Prescribing Practices
• Ongoing Review and Data Analysis to Ensure Continued Success
• Transparent Reporting and Outcomes
• Safety Bundle Recommendations
Project Goals:
- 10% Reduction of ALL Antibiotic Usage
- 10% Reduction in Broad Spectrum Antibiotic Use

Project Elements:
- Hospital Recruitment (Mar 2015)
- Identification of Champions
- Intake Questionnaire Completion
- Kick-Off Workshop (Aug 2015)
- Coaching Calls Monthly
- Site Visits
- Program Wrap-Up (Oct 2016)

Broad Spectrum Antibiotic Days Of Therapy:
- 24 Hospitals achieved a decrease in Broad Spectrum antibiotic use
- 19 Hospitals achieved the 10% reduction goal
- 5 Hospitals achieved a 1-9% reduction
- 4 Hospitals showed an increase in Broad Spectrum antibiotic use
- 14 hospitals saw a decrease in both total DOT and broad spectrum DOT
- Only 3 hospitals had an increase in both total DOT and broad spectrum DOT

Total Antibiotic DOT:

<table>
<thead>
<tr>
<th></th>
<th>Antibiotic DOT Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASC Baseline</td>
<td>735</td>
</tr>
<tr>
<td>ASC Current Period (Jun-Aug)</td>
<td>694</td>
</tr>
<tr>
<td>Relative Percent Change</td>
<td>-5.9%</td>
</tr>
</tbody>
</table>

Total Broad Spectrum Antibiotic DOT:

<table>
<thead>
<tr>
<th></th>
<th>Broad Spectrum DOT Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASC Baseline</td>
<td>21.7</td>
</tr>
<tr>
<td>ASC Current Period (Jun-Aug)</td>
<td>26.7</td>
</tr>
<tr>
<td>Relative Percent Change</td>
<td>-5.6%</td>
</tr>
</tbody>
</table>

Top Five Broad Spectrum Antibiotics:

<table>
<thead>
<tr>
<th></th>
<th>Ceftriaxone</th>
<th>Ciprofloxacin</th>
<th>Gentamicin</th>
<th>Levofloxacin</th>
<th>Moxifloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASC Baseline DOT</td>
<td>54.2</td>
<td>34.8</td>
<td>18.6</td>
<td>10.3</td>
<td>26.3</td>
</tr>
<tr>
<td>Current Period (Jun-Aug)</td>
<td>34.8</td>
<td>20.5</td>
<td>27.0</td>
<td>81.3</td>
<td>22.1</td>
</tr>
<tr>
<td>Relative % Change</td>
<td>-36.1%</td>
<td>-42.4%</td>
<td>-34.0%</td>
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<td>-34.0%</td>
<td>30.0%</td>
<td>3.7%</td>
</tr>
</tbody>
</table>
Summary:
• 5% decrease for Total Antibiotic use
• 13.5% decrease for Broad Spectrum antibiotic use
• 36% decrease in Levaquin use

Strengths:
• Vision to address a national problem
• The professionalism and dedication of participants
• The ability and willingness to submit data into the collaborative
• WVHA ability to formulate meaningful reports
• Willingness to adapt as new information becomes available e.g., Black box warning for Levaquin
• Willingness to share ideas and best practice opportunities e.g., Share best features of antibiogram

Challenges:
• Influencing physicians and other prescribers
• Patient expectations for antibiotics
• C. Difficile measurement
• Standardization of antibiogram
• Funding prioritization

Opportunities:
• Standardized collaborative antibiogram
• Decrease outpatient antibiotic prescribing
• Decrease urgent care antibiotic prescribing
• Coordination with nursing homes to decrease unnecessary antibiotic prescribing
• Ongoing potential for further refinement/decrease total and broad spectrum antibiotic use
• Decrease in resistant bacteria (MRSA)
• Decrease Clostridium Difficile
• Increase in Rapid Diagnostic Testing

Sustainability:
• 41 hospitals currently participating in the WVHA Antibiotic Stewardship Reporting Program
• Monthly reporting of facility wide utilization, as well as days of therapy by antibiotic/by practitioner
• Sustained the improvements achieved during the collaborative

Any questions?
Valerie Jividen
vijividen@wvha.org
Outpatient Antimicrobial Stewardship

Antibiotics are prescribed in 21% of all pediatric ambulatory visits.
Results in ~44 million prescriptions.
Respiratory conditions account for ~72% of these visits.
In 23% of the visits when antibiotics were prescribed for respiratory conditions, antibiotics are not clearly indicated.
Accounts for >10 million prescriptions annually.
Outpatient Antimicrobial Stewardship

- What’s the big deal??
- Antibiotic adverse reactions
- Costs
- Antibiotic resistance
- Association with other illnesses/conditions.

Antimicrobial Stewardship in the Outpatient Setting

- Over 180,000 unplanned medical visits/year for antibiotic-related adverse events in children
- Leads to substantial potential morbidity and cost.
- Side effects can be:
  - Mild – Diarrhea, Rash
  - More Severe – Stevens Johnson Syndrome
  - Life Threatening – Anaphylaxis

Antibiotic Expenditures in the United States by Treatment Setting

- Total 2008 cost: $10.3 billion
- 51% community
- 34% hospitals
- 15% nursing homes

Estimate 60-70% of antibiotic use occurring in outpatient setting.

Costs

- Jick et al compared 160,000 US children (less than 10 yo) with private insurance to a similar number of children in the UK in 2009
- 75% in US cohort received 1 or more antibiotic prescriptions vs. 50% in UK
- The estimated annual cost in the US was 5x greater
  - $2.5 million vs. $477,000

Antibiotic Resistance

Alexander Fleming

- "The greatest possibility of evil in self-medication is the use of too small doses so that instead of clearing up infection the microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out which can be passed to other individuals and from them to others until they reach someone who gets a septicemia or pneumonia which penicillin cannot save."

(New York Times June 26, 1945)

Beatrice the Biologist
Antibiotic Resistance

- Antibiotic resistant infections:
  - Require prolonged or costlier treatments
  - Extend hospital stays
  - Necessitate additional doctor visits and healthcare use
  - Result in greater disability and death
- Total economic cost (estimated):
  - $20 billion/year in direct costs
  - $35 billion/year if loss of productivity included

Antibiotic Resistance

- Use of antibiotics is the single most important factor leading to antibiotic resistance.
- Antibiotics are among the most commonly prescribed drugs.
- Up to 50% of antibiotics prescribed are not needed or are not optimally effective as prescribed.

Antibiotic Resistance Threats in the US

Estimated minimum number of illnesses and deaths caused by antibiotic resistance:

- At least 2,049,442 illnesses
- At least 23,000 deaths

Antibiotic Resistance Threats in the US

Estimated minimum number of illnesses and deaths due to *Clostridium difficile* (C. difficile), a unique bacterial infection that, although not significantly resistant to the drugs used to treat it, is directly related to antibiotic use and resistance:

- At least 250,000 illnesses
- At least 14,000 deaths

Antibiotic Resistance

WHO Warnings of Increasing Antibiotic-Resistant

- Antibiotic-resistant organisms are a huge problem, and it’s getting worse.
- Antibiotic-resistant organisms are on the rise. World Health Organization

Antibiotic-resistant genes

- Antibiotic-resistant genes are on the rise. World Health Organization

US first: E coli resistant to both colistin, carbapenems

- Resistance to the Antibiotic of Last Resort Is Silently Spreading
- Colistin-resistant nxr-1 E. coli Discovered in US

Stat
- Suspending Resistant to Last-Resort Antibiotic Arzinis China
- Colistin was never approved and sold in China
CDC – Urgent Threats

MICROORGANISMS WITH A THREAT LEVEL OF URGENT

Cholera
Vibrio cholerae

Listeria
Listeria monocytogenes

Curthlostridium difficile

CDC 2013

CDC – Serious Threats

MICROORGANISMS WITH A THREAT LEVEL OF SERIOUS

MRSA
Methicillin-resistant Staphylococcus aureus

VRE
Vancomycin-resistant Enterococcus

ESBL
Extended-spectrum β-lactamase-producing Enterobacteriaceae

CDC 2013

CDC – Concerning Threats

MICROORGANISMS WITH A THREAT LEVEL OF CONCERNING

Vancomycin-resistant Staphylococcus aureus (VRSA)

Erythromycin-resistant Group A Streptococcus

Clindamycin-resistant Group B Streptococcus

CDC 2013

# of New Antibacterial Drug Application (NDA) Approvals by Year Intervals

The number of new antibiotics developed and approved has mostly decreased in the past three decades, leaving fewer options to treat resistant bacteria.

CDC 2013

Antibiotics, Pediatric Dysbiosis, and Disease

- Epidemiologic data suggests an association between early antibiotic use and disease phenotypes
- Antibiotic use in infancy induces imbalances in gut microbiota (dysbiosis)
- The gut microbiome plays a key role in nutrition, metabolism, and the development of the immune system

Cell Host and Microbe, 2016, 17

Conditions Associated With Antibiotic Use in Children

- Asthma
- Eczema
- IBD
- JIA
- Obesity
Principles of Judicious Antibiotic Prescribing for Bacterial URIs In Pediatrics

1. Determine the likelihood of a bacterial infection
2. Weigh benefits vs. harms of antibiotics
3. Implement judicious prescribing strategies

Determine the Likelihood of a Bacterial Infection (AOM)

- Requires middle ear effusion and signs of inflammation:
  1. Moderate to severe bulging of the TM, or
  2. Otorrhea not due to otitis externa, or
  3. Mild bulging of the TM with ear pain or intense erythema of the TM.

Otitis Media

Determine the Likelihood of a Bacterial Infection – Acute Bacterial Sinusitis

- Persistent symptoms without improvement
  - Nasal discharge or daytime cough>10 days
- Worsening symptoms
  - New onset fever, daytime cough, or nasal discharge after improvement of viral URI.
- Severe onset
  - T 39°C or greater, purulent nasal discharge.

Determine the Likelihood of a Bacterial Infection– Acute Pharyngitis

- Diagnosis of GAS pharyngitis requires confirmation by rapid testing or culture
- Only test if two of the following are present:
  - Fever
  - Tonsillar exudate/swelling
  - Swollen/tender anterior cervical lymph nodes
  - Absence of cough
- Do not treat empirically
- Colonization rates of GAS can reach 15-20% even among asymptomatic children

Determine Likelihood of Bacterial Infection– Colds, URIs, Acute Cough Illness, Bronchitis

- Symptoms may overlap bacterial URIs
- Account for millions of office visits/yr
- Acute bronchitis- diagnosis > 2 million/yr, Treated with antibiotics >70% of the time
- Focus on symptomatic relief
- Antibiotics should not be prescribed
**Antibiotics: Benefits vs. Harms – AOM**

- At least half of patients with AOM will recover without antibiotics.
- Recovery is more likely and hastened with antibiotics (vs. placebo).
- Recovery is less likely without antibiotics for:
  - Younger children
  - Bilateral disease
  - Those with more severe signs and symptoms

**Recommendations for Initial Management for Uncomplicated AOM**

<table>
<thead>
<tr>
<th>Age</th>
<th>Stereotyping</th>
<th>Bilateral AOM</th>
<th>Bilateral with Strep</th>
<th>Bilateral without Strep</th>
<th>Bilateral AOM without Strep</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 mos to 2 y</td>
<td>Antibiotic therapy</td>
<td>Antibiotic therapy</td>
<td>Antibiotic therapy</td>
<td>Antibiotic therapy or additional observation</td>
<td>Antibiotic therapy or additional observation</td>
</tr>
<tr>
<td>6-11 y</td>
<td>Antibiotic therapy</td>
<td>Antibiotic therapy</td>
<td>Antibiotic therapy</td>
<td>Antibiotic therapy or additional observation</td>
<td>Antibiotic therapy or additional observation</td>
</tr>
</tbody>
</table>

- A cautionary note: If symptoms persist or change, seek medical attention if there is no improvement or if there is worsening of symptoms.
- Care should be taken to avoid unnecessary antibiotic use and to promote appropriate use.

**Antibiotic Benefits vs. Harms – Acute Bacterial Sinusitis**

- 2 of 3 studies published since 1998 showed a significantly improved likelihood of symptom resolution after 3 and 14 days.
- The study that showed no significant difference used less stringent diagnostic criteria.
- Antibiotics benefit in preventing complications (e.g., orbital cellulitis, intracranial abscess) or is proven.
- AAP recommends treatment with antibiotics in children with clinical acute bacterial sinusitis, especially in those with severe or worsening symptoms.

**Antibiotics Benefits vs. Harms – GAS Pharyngitis**

- Strong evidence that antibiotics shorten the duration of symptoms by about 1 day.
- Treatment may reduce horizontal transmission.
- Historically for the prevention of rheumatic fever.
- May help prevent supplicative complications (peritonsillar abscess, AOM, sinusitis).
- One study suggested the NNT to prevent 1 episode of PTA is > 4000.

**Implement Judicious Prescribing Strategies**

- Right antibiotic
- Right dose
- Right duration
Antibiotic Treatment of AOM

Antibiotic Treatment of Acute Bacterial Sinusitis
- First line: high dose amoxicillin
- May use high dose amoxicillin/clavulanate for:
  - Moderate to severe illness
  - Children < 2 years old
  - Day care attendees
  - Recently treated with antibiotics
- Ceftriaxone if vomiting, unable to tolerate oral meds, or noncompliant patients
- With penicillin allergy treat with cefdinir, cefpodoxime, or cefuroxime (S pneumoniae susceptibility 60-75%)

Antibiotic Treatment of GAS Pharyngitis

Duration of Antibiotic Therapy – AOM
- Children < 2 yo or those with severe disease – 10 days
- Children 2-5 yo with mild-moderate disease – 7 days
- Children > 5 yo with mild-moderate disease – 5 to 7 days

Duration of Antibiotic Therapy – Sinusitis
- Optimal duration has not received systematic study
- Recommendations vary from 10 days to 28 days
- Treat for 7 days after patient becomes free of symptoms

Kronman Paper
- Meta-analysis of pediatric studies published 2000-2011 to determine ARTI bacterial prevalence rates
- Retrospective cohort analysis of children < 18 yo in ambulatory clinics sampled by the 2000-2010 National Ambulatory Medical Care Survey to determine estimated US ARTI antimicrobial prescribing rates,
Kronman Paper

- AOM bacterial prevalence-64.7%
- Pharyngitis GAS positive-20.2%
- Sinusitis bacterial prevalence-78%
- No URI of bronchitis study met inclusion criteria
- Conclusion-An estimated 27.4% of children with an ARTI have a bacterial illness
- Antibiotics were prescribed in during 56.9% of ARTI encounters
- Marshall Pediatrics-48.4%

Profile of a High Frequency Prescriber

- ER and UCC docs> family docs> pediatricians
- Increased years from med school graduation
- Staff physicians> residents
- Nonteaching institutions
- South

Counties with an increased proportion of:
- Obesity
- Infants and children 2yo and younger
- Prescribers per capita
- Females

Profile of the Patient that Receives Antibiotics

- White
- Southern
- Ages 12-18 years(compared to 6-12yo).
- Arrive later in the morning and the afternoon.

Who Gets Broad Spectrum Antibiotics?

- Those with respiratory conditions in which antibiotics are not indicated.
- Younger patients (<6yo vs. 6-12yo)
- Patients in the south
- Private insurance

Drivers of Inappropriate Antibiotic Prescribing

- Patient Satisfaction/Pressure
- Time Constraints
- Diagnostic Uncertainty
- Externalized Responsibility
- Fear of Serious Complications
Patient Satisfaction

- 272 patients (adults and children) presenting to ten academic ERs with symptoms of an ART were enrolled.
- 68% of bronchitis patients and 9% of URI patients received antibiotics
- Physicians were more likely to prescribe antibiotics when they believed patients expected them
- Physicians were only able to identify 27% of patients expecting antibiotics

Patient Satisfaction

- Satisfaction with the visit was reported by 87% of patients that received antibiotics and 89% of those not receiving antibiotics.
- Satisfaction reported by 92% of patients that had a better understanding of their visit but only 72% of those who thought they had no better understanding.

Patient Satisfaction

- 2011 parent focus group in Cambridge, MA published in 2014
- Participants understood that antibiotics do not treat viruses
- Stated reluctance to overuse antibiotics
- Their reluctance was related to the development of resistance
- Most believed antibiotics were needed to treat AOM

Relationship Between Time Spent in an Encounter With the Use of Antibiotics for Viral ARTs

- Mean number of minutes spent with a pediatric patient with a URI or bronchitis that resulted in a prescription for antibiotics – 14.24 minutes
- Without antibiotics prescribed – 14.16 minutes
- Results were controlled for patient age, race, sex, insurance or whether the physician was the patient’s primary care physician.

Diagnostic Uncertainty

- Bacterial vs. Viral Infection
- Providers perceiving minimal risks with antibiotics are more likely to prescribe them

Externalized Responsibility

- Physicians acknowledge the problem
- It’s not me, it’s you!
Fear of Serious Complications

- Bacteremia in healthy toddlers is now a rare event.
- Pneumococcal bacteremia rates in febrile 3-36 month olds-3.5/100,000.

Strategies to Improve Antibiotic Prescribing Practices

- Physician commitment letters
- Behavioral interventions
- Education, audit and feedback

Physician Commitment Letters

- Framed poster sized physician commitment letters were placed in exam rooms.
- Results: posted commitment letters resulted in a 19.7% decrease in inappropriate antibiotic prescribing relative to controls.
- No evidence of coding shift and rates of appropriate antibiotic prescribing did not decrease.

Behavioral Interventions

- Meeker et al. looked at behavior interventions on inappropriate antibiotic prescribing.
- All clinicians received education on antibiotic prescribing guidelines.
- Three behavioral interventions were used alone or in combination:
  - Suggested alternatives
  - Accountable justification
  - Peer comparison

Results: Antibiotic Prescribing Rates for Antibiotic-Inappropriate ARTIs Before and After Intervention

<table>
<thead>
<tr>
<th>Intervention Type</th>
<th>Before Intervention</th>
<th>After Intervention</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>control group</td>
<td>24.2%</td>
<td>13.1%</td>
<td>-11.1%</td>
</tr>
<tr>
<td>suggested alternatives</td>
<td>22.8%</td>
<td>6.7%</td>
<td>-16.1%</td>
</tr>
<tr>
<td>accountable justification</td>
<td>22.2%</td>
<td>5.2%</td>
<td>-17.0%</td>
</tr>
<tr>
<td>peer comparison</td>
<td>19.9%</td>
<td>3.7%</td>
<td>-16.2%</td>
</tr>
</tbody>
</table>

Decrease in prescribing rates were significant for accountable justification and peer comparison

Education with Audit and Feedback

- 1 hour clinician education session.
- Quarterly audit and feedback of prescribing for bacterial and viral ARTIs or usual practice.
- Broad spectrum antibiotic prescribing decreased from 26.8% to 14.3% (controls 28.4% to 22.6%).
- Off guideline prescribing decreased:
  - Pneumonia-15.7% to 4.2%
  - Sinusitis-38.9% to 18.8%
  - Pharyngitis and viral infections were essentially unchanged.
**Effect of Education Plus Audit and Feedback on Rates of Prescribing Broad Spectrum Antibiotics**

![Graph showing the impact of education and feedback on antibiotic prescribing rates over time.](image1)

**Effect of Stopping Audit and Feedback on Prescribing Broad Spectrum Antibiotics**

![Graph showing the impact of stopping audit and feedback on antibiotic prescribing rates over time.](image2)

---

**Acute Bronchitis – A Tough Nut to Crack**

- Acute bronchitis—Cough-predominant ARTI of less than three weeks duration.
- Antibiotics have been shown not to be effective for 40 years.
- Between 1980–1999, antibiotic prescribing rate 60%-80%.
- For the last 15 years, the CDC led efforts to decrease antibiotic prescribing for bronchitis.
- Since 2005 a HEDIS measure has stated that the antibiotic prescribing rate for bronchitis should be zero.

---

**Effect of CDC Efforts and HEDIS Measures on Antibiotic Prescribing Rates for Bronchitis**

![Graph showing the impact of CDC efforts and HEDIS measures on antibiotic prescribing rates for bronchitis.](image3)

---

**Vaccines**

- PCV7 introduced in US in 2000
- PCV13 in 2010
- Influenza
- Hib
- Others

---

**Our Study**

- Reviewed 200 charts for each physician working in the office (100 charts) and Now Care (100 charts).
- Charts reviewed if patients presented with and combination of these symptoms—nasal congestion, cough, sore throat, earache, fever.
- Recorded patient’s age, symptoms, diagnosis and if antibiotics was prescribed.
- Also recorded:
  - Whether the antibiotic prescribed was appropriate per guidelines.
  - Whether antibiotics were appropriate for the diagnosis listed.
  - Did the documentation in the chart support the diagnosis.
Number of Antibiotics Prescribed in the Office Setting vs. Now Care

- Now Care - 582 prescriptions
- Office - 581 prescriptions

% of Patients Receiving Antibiotics per Specific Physician

% of Patients Receiving the Recommended Antibiotic per Specific Physician

Diagnosis by Doctor

% antibiotic prescribed pre - post audit/feedback, peer comparison

% recommended antibiotic prescribed pre - post audit/feedback, peer comparison
National Action Plan for Combating Antibiotic-Resistant Bacteria (March 2015)

- Reduce inappropriate antibiotic use by half in outpatient settings by 2020
- Reduce by 20% in inpatient settings
- Requires federal agencies and others to expand quality measures for antibiotic prescribing
- Within 3 years CMS plans to expand the Physician Quality Reporting System to discourage inappropriate antibiotic use to treat nonbacterial infections such as respiratory tract infections
- The CDC is to support health departments in creating state antibiotic stewardship programs.

New Societal Approaches to Empowering Antibiotic Stewardship

- Antibiotics lose efficacy over time
- Antibiotic-resistant bacteria are transferred from patient to patient
- Every patient's use of antibiotics affects the future ability of every other patient to use those same antibiotics
- Antibiotics are a shared community trust

New Societal Approaches to Empowering Antibiotic Stewardship

- Misuse of antibiotics does not just harm the individual, it has a negative health effect on everyone
- The indulgence of individual practitioner freedom regarding antibiotic choices must be tempered by the knowledge that inappropriate use of antibiotics affects society at large.
- Making data on antibiotic prescribing patterns publically available will help support stewardship initiatives.

New Societal Approaches to Empowering Antibiotic Stewardship

- The crisis of antibiotic resistance continues to worsen
- The alternative to meaningful change is continuation of a problem and entry into a prolonged post-antibiotic era
- Results in increased morbidity and mortality from antibiotic resistant infections
- Time to develop new clinical and societal approaches to empower effective and sustainable antibiotic stewardship.

Closing Thoughts

"It's all in the presentation."
Closing Thoughts

- Quit trying to find a reason to give antibiotics and consider reasons to not give an antibiotic.
- Consider the big picture.

References

- Hicks et al. Clinical infectious Diseases, 2015;60(9):1308-1316.
- Linder J. JAMA Internal Medicine, 2014;174(12):2029-2030.
- Goos A, Maloua A. Archives of Pediatric and Adolescent Medicine, 2005;159(12):1145-1149.
Antibiotic Stewardship
Optimizing Antibiotic Use and Patient Outcomes

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Faculty Disclosures
- The speaker has no financial relationship(s) or disclosures.
- The conclusions in this talk are the speaker's and do not necessarily represent the Centers for Disease Control and Prevention.

Objectives
- Review adverse events associated with antibiotic use.
- Describe the current state of antibiotic use in the United States.
- Present an overview of the core elements of antibiotic stewardship.

Antibiotic use saves lives.
- Once deadly, most infectious diseases are treatable, substantially reducing deaths compared to the pre-antibiotic era.
- Antibiotics are important adjuts to modern medical advances;
  - Surgeries
  - Dialysis
  - Transplants
  - Cancer therapies

Antibiotic use can lead to unintended consequences and adverse events.
- Adverse events from antibiotics range from minor to severe, and affect multiple body systems;
  - Allergic reactions, including anaphylaxis (life-threatening)
- Antibiotics were the second most common cause of adverse drug events (16.1%) leading to emergency department visits.
  - Antibiotics accounted for 7 out of 10 of the top drugs implicated in drug-related emergency department visits for children (2 out of 10 for all age groups).

Antibiotic use and microbiome disruption leads to Clostridoides difficile infection.
- CDI is one of the most commonly reported healthcare-associated infection.
  - CDI caused 29,000 deaths in the U.S. in 2011.
  - The estimated acute care cost attributable to CDI is to be $1.2-5.9 billion annually.
- Risk of C. difficile infection, morbidity and mortality is highest in older adults.
- Some evidence suggests higher rates of sepsis in people who have received antibiotics.

Antibiotic use at the individual and population level contributes to the development of antibiotic resistance.
- Antibiotic resistance is never far behind the introduction of a new antibiotic.
- Bacteria will inevitably develop ways to resist new antibiotics developed.
- Antibiotic use is the most important modifiable risk factor leading to antibiotic resistance.
Antibiotic resistant infections can happen anywhere.

- Most antibiotic resistant infections occur in the community, most deaths related to antibiotic resistant infections occur in the hospital and nursing home settings.
- Patients with antibiotic resistant infections have:
  - Higher mortality
  - Worse outcomes
  - Higher healthcare cost:
    - Annual excess direct healthcare cost: $20 billion
    - Additional annual cost of lost productivity: $19 billion

Antibiotic Expenditures for Humans in the United States by Treatment Setting 2010-15: Total $36.0 billion

Approximately 85%-95% of human antibiotic use by volume occurs in outpatient setting.

Inappropriate antibiotic use includes:

- Unnecessary antibiotic use
- Improper antibiotic selection
- Errors in antibiotic duration
Outpatient antibiotics are prescribed at higher rates in West Virginia than the National Average for children and adults in 2016.

**Kids <20 years**
- United States: 790
- West Virginia: 1327

**Adults ≥20 years**
- United States: 852
- West Virginia: 1236

Antibiotic Prescriptions per 1000 population

Amoxicillin with or without clavulanate is the first-line recommended agent for sinusitis.

- Antibiotic Selection for Sinusitis — United States, 2000-11

- Percent of Visits with Antibiotic in the South vs. other regions.

Antibiotic-inappropriate respiratory illnesses receive more antibiotics in the South than other regions.

- Percent of visits for antibiotic-inappropriate respiratory illnesses that received antibiotics, MarketScan 2014

Antibiotic prescribing for antibiotic-inappropriate acute respiratory illnesses (ARIs)* by outpatient setting — MarketScan, 2014

- Overall nationally: 755 days of antibiotic therapy per 1000 patient-days.

- Truven MarketScan Hospital Drug Database, 2006-2012
- 300-383 hospitals contributing data per year
- Over 34 million discharges
- 55% of patients received at least one dose of antibiotics during their visit.
While overall rates of antibiotics use did not change from 2006-12, use of certain antibiotics of concern increased significantly.

Antibiotic use in acute care hospitals is high in the South Central Region.

Assessing appropriate antibiotic use in hospitals is very challenging.

- CDC, The Pew Charitable Trusts, and stewardship experts identified key targets to support the goal of reducing inappropriate hospital antibiotic use by 20% by 2020.
  - Two agents: Vancomycin, fluoroquinolones
  - Two infections: Community-acquired pneumonia, urinary tract infections

The nursing home population is expected to grow.

- More than 7 million Americans receive care or reside in ~15,600 CMS-certified NH every year.1
  - By 2040 the number of Americans ≥ 65 years will double to more than 90 million.2
  - 35% of those ≥ 65 years will receive NH care in their lifetime.3
- Residents in NHs have increasingly complex medical conditions.4

Nursing Home Antibiotic Use-National pharmacy transaction data

- Analysis of national antibiotic transaction data in 2014:1
  - Over 14 million antibiotic transactions
  - 85% were oral antibiotics
  - Rates higher in those <65 years
  - Fluoroquinolones accounted for 22% of all antibiotic transactions
  - Highest rate of antibiotic use in the South Census Region

Nursing Home Antibiotic Use-Electronic health record data

- Analysis of antibiotic orders in electronic health records in ~3300 nursing homes 2015-2017:1
  - 51% residents receive at least one antibiotic order during their nursing home stay
  - In 2017, average antibiotic prescribing rate was 109 days of therapy/1000 resident days
  - Levofoxacin was the most commonly prescribed antibiotic
  - UTI was the most common indication, followed by respiratory and skin and soft tissue infections
  - 30% of prescriptions were ordered on transfer from the hospital
Nursing Home Antibiotic Use-CDC prevalence survey

- Single day survey of antibiotic use in 9 NHs1
  - 11.3% of all residents were on an antibiotic
    - 95% (9.4-13.9%) of antibiotic use was for prophylaxis
    - 23% of antibiotic use was for short-stay residents (21.2%) and residents with devices (23.5%)
  - Experience informed larger prevalence survey conducted in 161 nursing homes (>15,000 residents) to describe overall antibiotic use and prescribing practices for UTI

Fluoroquinolone Prescribing

- FDA issued a boxed warning that fluoroquinolones should not be used for acute bacterial sinusitis, acute bacterial exacerbations of chronic bronchitis, and uncomplicated urinary tract infections when other treatment options are available.
- In these conditions, the risks of serious adverse events generally outweigh the benefits of treatment with fluoroquinolones.

Examples of Antibiotic Stewardship Targets

<table>
<thead>
<tr>
<th>Category</th>
<th>Nursing Homes</th>
<th>Outpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most frequent diagnoses leading to antibiotic prescribing</td>
<td>Pyelonephritis (36%)</td>
<td>UTI (26%)</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection (UTI) (13%)</td>
<td>Pyelonephritis (35%)</td>
</tr>
<tr>
<td></td>
<td>Skin and soft tissue infections (25%)</td>
<td>Skin and soft tissue infections (18%)</td>
</tr>
<tr>
<td></td>
<td>Urethritis (25%)</td>
<td>Urethritis (17%)</td>
</tr>
<tr>
<td>Antibiotics of concern</td>
<td>Fluoroquinolones</td>
<td>Fluoroquinolones</td>
</tr>
<tr>
<td></td>
<td>3rd- and 4th-generation cephalosporins</td>
<td>Macrolides</td>
</tr>
<tr>
<td></td>
<td>Carbapenems</td>
<td>Fluoroquinolones</td>
</tr>
<tr>
<td></td>
<td>Beta lactam/beta lactamase inhibitor combinations</td>
<td>Monobactams</td>
</tr>
</tbody>
</table>

Transitions and Duration of Therapy

Antibiotic Stewardship can improve outcomes and reduce infection with antibiotic-resistant bacteria and C. difficile

- Cochrane review of interventions to improve antibiotic prescribing for hospitalized patients:
  - Improved antibiotic prescribing without difference in mortality and a likely reduced length of stay
- A systematic review and meta-analysis that included 32 studies in hospitalized patients:
  - Antibiotic stewardship programs reduce the incidence of infection and colonization with MDRs and C. difficile infection
- An ecologic analyses examined site-specific antibiotic prescribing rates and community-associated C. difficile infection rates:
  - Reducing outpatient antibiotic prescribing by 30% could reduce community-associated C. difficile infection by 17%

Sources:
Conclusions

- We need to improve antibiotic prescribing across the healthcare spectrum.
  - Outpatient: At least 30% of antibiotic prescriptions in the United States are unnecessary.
  - Hospitals: Antibiotic use has not changed, but use of agents of concern have increased.
  - Nursing homes: Antibiotic use for urinary tract infections and the use of fluoroquinolones are key antibiotic stewardship targets.
- CDC's Core Elements of Antibiotic Stewardship provides a framework for improving antibiotic prescribing across the spectrum of healthcare.

Questions or Comments
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Faculty Disclosures

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Objectives

- Review outpatient antibiotic prescribing rates in adults and pediatrics.
- Identify best practices for optimizing outpatient antibiotic use.
- Describe the effect of core elements implementation on antibiotic prescribing for acute respiratory infections.

Have we made any progress in improving antibiotic use?
Outpatient antibiotic prescribing rates to children decreased 13.5% but rates for adults have been stable.

Lesson learned: Vaccines are key antibiotic stewardship tools.

Lesson Learned: Public health and pediatric clinicians helped improve antibiotic use in children by working together.

Viruses or Bacteria? What's got you sick?

- An antibiotic will not make you feel better if you have a virus.

Clinicians generally know the guidelines for common outpatient infections. Education and guidelines are important, but alone they are not very effective.

What are the main factors that affect antibiotic prescribing?
Clinicians cite diagnostic uncertainty and fear of infectious complications as reasons to prescribe antibiotics inappropriately.

Communicating about adverse events to clinicians and patients is key.

Clinicians cite patient demand for antibiotics and concern about losing patients as a reason they prescribe antibiotics when they shouldn’t.

Strategy: Communication training can help keep patients satisfied without antibiotics.

Clinicians can effectively and efficiently communicate with patients when antibiotics are not needed.

- Review physical exam findings
- Deliver a clear diagnosis
- Provide a two-part, negative-then-positive recommendation
- Provide a contingency plan

CDC has a communication module available with free CE

Module 6 of CDC Training on Antibiotic Stewardship
https://www.train.org/cdctrain/training_pln/3697

COME ELEMENT: EDUCATION AND EXPERTISE

Habit, decision fatigue, and other social and emotional factors impact antibiotic prescribing behaviors.

Antibiotic prescribing isn’t always rational, so we need help from behavioral science.

Nudge
PHILOSOPHY OF NUDGE
FLESHING OUT THE PHILOSOPHY
EYEWITNESS INVESTIGATIONS
BY DANIEL KAHNEMAN
Public commitment posters can reduce inappropriate antibiotic prescriptions.

**Core Element: Commitment**

Your health is important to me.

![Image of commitment poster](image)

**Commitment Poster: Results**

<table>
<thead>
<tr>
<th>Antibiotic Prescribing Rate</th>
<th>Baseline</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>70%</td>
<td>50%</td>
</tr>
<tr>
<td>Poster</td>
<td>40%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Adjusted difference in differences: -20% (96 to 33%)

---

Tracking and Reporting with Peer Comparisons

**Core Element: Tracking and Reporting**

- You: [Graph showing antibiotic use, not legible]
- Network: [Graph showing antibiotic use, not legible]

![Graph of antibiotic use by clinicians](image)

**Tracking and Reporting with Peer Comparisons**

"You are a Top Performer"  "You are not a Top Performer"

You are in the top 10% of clinicians. You wrote 0 prescriptions out of 21 acute respiratory infection cases that did not warrant antibiotics.

Your inappropriate antibiotic prescribing rate is 15%. Top performers' rate is 0%. You wrote 3 prescriptions out of 20 acute respiratory infection cases that did not warrant antibiotics.

---

Peer Comparison: Results

![Graph showing peer comparison](image)

Antibiotic prescribing is a behavior as much as a clinical decision.

**Strategy:** Behavioral change strategies can be leveraged in effective antibiotic stewardship interventions.
Behavioral science approaches to antibiotic stewardship can be used across the spectrum of healthcare.

Do Core Elements of Outpatient Antibiotic Stewardship improve antibiotic use and patient outcomes?

14 VHA clinics implemented Core Elements to improve antibiotic use for acute respiratory infections (ARIs).

- Data from 2014-2018
- 14 clinics and 1,357 providers
- Staggered roll out of intervention
  - 4 sites in 2015
  - 10 sites in 2017
- Total ARI visits included
  - Pre-intervention: 29,782
  - Post-intervention: 8,369

Sites demonstrated commitment by recruiting stewardship champions at all sites.

Academic detailing was used to fulfill action for policy and practice.

Antibiotic prescribing was tracked and reported back to providers at all sites.
Education and expertise were provided to healthcare providers and patients at all sites.

Interventions resulted in decreases in antibiotic prescription rates for all ARIIs.

Percent change in antibiotic prescribing per-visit for ARIIs by diagnosis post-intervention compared to pre-intervention:

- Sinusitis: -11%
- Pharyngitis: -25%
- Bronchitis: -26%
- All uncomplicated ARIIs: -23%

Reductions were statistically significant.
Prevalence rate ratio for antibiotic prescribing for ARI post versus pre-Intervention:

- Bronchitis: 0.49
- Pharyngitis: 0.29
- Sinusitis: 0.87
- All uncomplicated ARIIs: 0.52

Interventions were safe, and adverse events were less frequent after the intervention.

Frequency of patient outcomes for ARI visits as absolute percent difference and risk ratio post-intervention compared to pre-intervention:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Percent difference, absolute</th>
<th>Risk Ratio* (95% confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day ARI-related visits</td>
<td>0.07%</td>
<td>1.02 (0.95, 1.13)</td>
</tr>
<tr>
<td>30-day hospitalizations</td>
<td>0.01%</td>
<td>1.15 (0.57, 2.34)</td>
</tr>
<tr>
<td>30-day adverse drug events</td>
<td>-0.29%</td>
<td>0.96 (0.76, 0.94)</td>
</tr>
<tr>
<td>30-day C. difficile infection</td>
<td>0.04%</td>
<td>**</td>
</tr>
</tbody>
</table>

*Adjusted for covariate effects.
**Negative model deviance change.

Conclusions

- Antibiotic stewardship can help optimize antibiotic prescribing:
  - Education alone is unlikely to be effective.
  - Communication training can improve outpatient antibiotic prescribing.
  - Interventions informed by behavioral science can improve antibiotic prescribing.
- Core Elements of Outpatient Antibiotic Stewardship can reduce antibiotic use for acute respiratory infections, many of which do not require antibiotics.
  - Antibiotic stewardship efforts were safe and did not affect 30-day revisits or hospitalizations.
  - The incidence of adverse drug events was lower after antibiotic stewardship was initiated.

Questions or Comments
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