Listeria Endocarditis

Claudia Summa BScPhm
Pharmacy Resident
Wednesday, May 16, 2007
Objectives

- To review a patient who presented with *Listeria* endocarditis
- To discuss features of *listeria monocytogenes* and pathophysiology of how this organism causes disease
- To describe epidemiology, complications, RF, s&sx associated with *listeria* endocarditis
- To discuss tx options available for *listeria* endocarditis
Patient Review

- Please refer to handout provided
Listeria Monocytogenes

- aerobic, GP coccobacillus
- facultative intracellular bacteria
- isolated from soil, dust, animal feed, water, sewage, and almost any type of animal cultured
- frequently found in raw & unprocessed food products (meats, vegetables, dairy and delicatessen products to be consumed without further heating)
- outbreaks associated with contaminated rice salad, coleslaw, soft cheese, hot dogs, shrimp, chocolate milk, and corn salad have been reported

Are We Colonised with *Listeria*?

- Transient colonizer of the human GIT

- Infection does not occur unless host factors for invasive disease are present, or the amount delivered to the intestinal tract is large enough to overwhelm local GI barriers

How Does *Listeria* Cause Disease?

- penetrating actively into a wide range of host cells (phagocytes, epithelial, parenchymal cells) → either phagocytosis or induced phagocytosis

- cluster of virulence genes → evasion of the phagocytic vacuole → listeria resides within the vacuole and multiplies within the cytoplasm

How Does *Listeria* Cause Disease?

1. **At the Cytoplasm:**
   Bacteria are wrapped with actin filament forming a comet like structure.

2. **Move across cytoplasm to the cell membrane.**

3. **Internalization**
   (hidden from humoral defense mechanisms & antibiotics)

Listeria Endocarditis

- Observed in about 8% of infected adults
- Mortality has been reported from 37-50%
- Subacute disease:
  - S&SX: fever, weakness, dyspnea, and cardiac murmur
  - Acute CHF found in 50% of pts
- etiologic diagnosis is confirmed by + blood cultures

Doganay M. *FEMS Immunology and Medical Microbiology*. 2003; 35: 173 –175.
Risk Factors for *Listeria* Endocarditis

- Neonates
- Pregnant women
- Elderly
- Patients with impaired cell mediated immunity
- Rheumatic heart disease, hypertrophic cardiomyopathy, mitral prolapse and ischemic cardiomyopathy

Doganay M. *FEMS Immunology and Medical Microbiology*. 2003; 35: 173 –175.
World Literature Review

- 57 case reports

- more ♂ than ♀ (1.6:1)

- Mortality ~ 37%
  - Pts without valve prosthesis → mortality of ~ 31%
  - Pts with previous valve prosthesis → higher mortality ~ 41%

- Survival rate: similar b/w Abx tx group alone & medical treatment + surgery

streptomycin + PCN $\rightarrow$ survival rate of 73%

AMG + PCN $\rightarrow$ survival rate of 63%
- same as penicillin alone

Experimental data: synergism b/w ampicillin or PCN + AMG against *listeria monocytogenes*

**Table 3  Antibiotic treatment and survival**

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Survived</th>
<th>Died</th>
<th>% Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloramphenicol + penicillin</td>
<td>1</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Erythromycin + chloramphenicol + oleomycin</td>
<td>1</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Co-trimoxazole</td>
<td>1</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Streptomycin + penicillin*</td>
<td>8</td>
<td>3</td>
<td>73</td>
</tr>
<tr>
<td>Penicillin*</td>
<td>7</td>
<td>4</td>
<td>64</td>
</tr>
<tr>
<td>Penicillin + aminoglycoside</td>
<td>10</td>
<td>6</td>
<td>63</td>
</tr>
<tr>
<td>Erythromycin + penicillin</td>
<td>1</td>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1</td>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

*Includes all types of penicillin, ie, benzyl penicillin, penicillin G, amoxycillin, and ampicillin.

Report of 2 Case & Reviews

- 68 pts reported in the medical literature
- Mean age ↑ from 47.1 yrs (1955-1984) to 65.5 yrs (1985-2000)
- 60% of pts → underlying valve disorder; of these 33.8% were prosthetic valves
- Most pts did not have hx of exposure to contaminated foods or materials

41.1% of pts → chronic debilitating conditions (diabetes, cirrhosis, alcoholism and impaired cell-mediated immunity)

16.2% of pts → severely immunocompromised by solid organ transplantation, leukemia or lymphoma, corticosteroid therapy, hemodialysis or AIDS

most often occurred on abnormal native or prosthetic valve, mainly on the aortic, mitral, or both valves (rarely seen in tricuspid valve)

Severe disease → 23 cases reported since 1975
- valvular dysfunction and murmurs were noted in 16 (69.6%) and 15 (65.2%) developed cardiac failure, meningitis was rarely seen in these patients

Report of 2 Case & Reviews: TREATMENT

- PCN OR ampicillin → most common
  - not completely bactericidal against *listeria*
  - in vitro PCN MICs are usually < 1mcg/mL, the MBC commonly exceeds 10 or more times that amount

- Role of gentamicin
  - synergistic activity in vitro and in vivo
  - in vivo synergism → not uniformly observed & retrospective clinical studies have not consistently shown better results for combined rather monotherapy

Report of 2 Case & Reviews: Treatment Outcomes

- 23/35 (65.7%) treated with combination of PCN + gentamicin or AMP + gentamicin survived

- 10/14 (71.4%) treated with PCN monotherapy survived

- Combination of vancomycin + gentamicin was successful in 4 patients

24 pts died (overall mortality 35.3%) → most occurred before 1985 and the mortality ↓ 12% in the last decade → ↑ use of surgery or more appropriate surgery

15/24 patients who had died had severe underlying diseases which may have worsened the prognosis

Report of 2 Cases & Reviews: Summary of Clinical Findings

### Table 1  Summary of most relevant clinical findings in patients with native and prosthetic valve endocarditis due to *Listeria monocytogenes*.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Native valve (45 patients)</th>
<th>Prosthetic valve (23 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>50</td>
<td>65.3</td>
</tr>
<tr>
<td>Males (%)</td>
<td>58.3</td>
<td>80</td>
</tr>
<tr>
<td>Underlying non-cardiac conditions (N)</td>
<td>23 (51.1%)</td>
<td>7 (30.4%)</td>
</tr>
<tr>
<td>Underlying cardiac disorders (N)</td>
<td>24 (53.3%)</td>
<td>23 (100%)</td>
</tr>
<tr>
<td>Site of valvular involvement (N)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitral</td>
<td>7 (15.6%)</td>
<td>12 (52.2%)</td>
</tr>
<tr>
<td>Aortic</td>
<td>12 (26.7%)</td>
<td>8 (34.8%)</td>
</tr>
<tr>
<td>Mitro-aortic</td>
<td>14 (31.1%)</td>
<td>3 (13.0%)</td>
</tr>
<tr>
<td>Tricuspid</td>
<td>2 (4.4%)</td>
<td></td>
</tr>
<tr>
<td>Tricuspid-aortic</td>
<td>1 (2.2%)</td>
<td></td>
</tr>
<tr>
<td>Not stated</td>
<td>9 (20.0%)</td>
<td></td>
</tr>
<tr>
<td>Overall mortality (N)</td>
<td>20 (44.4%)</td>
<td>5 (21.7%)</td>
</tr>
<tr>
<td>Treatment (N/total)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only medical</td>
<td>30/37 (81.1%)</td>
<td>11/22 (50.0%)</td>
</tr>
<tr>
<td>Mortality</td>
<td>12/30 (40.0%)</td>
<td>4/11 (36.4%)</td>
</tr>
<tr>
<td>Surgical</td>
<td>7/37 (18.9%)</td>
<td>11/22 (50.0%)</td>
</tr>
<tr>
<td>Mortality</td>
<td>3/7 (42.9%)</td>
<td>1/11 (9.1%)</td>
</tr>
</tbody>
</table>

*15 out of 45 (33.3%) patients with native valve endocarditis had a previously known underlying valve disorder.

*For a total of 59 patients for which treatment was clearly stated.

Resistance to *Listeria Monocytogenes*

- Streptomycin, tetracycline, chloramphenicol, & erythromycin (reported rarely) → resistance encoded by plasmids (most cases)

- Enterococcal plasmids encoding resistance determinants → easily transferred in vitro to *listeria*

- Most *listeria* strains have high resistance to cephalosporins (esp broad spectrum such as cefotaxime)
  - reason for resistance is lack of appropriate PBP in their cytoplasmic membrane

Killing Activity of Treatment Options

- **Bactericidal activity** → AMG, teicoplanin, vancomycin, and cotrimoxazole (which trimethoprim)

- **Bacteriostatic activity** → PCN, ampicillin, macrolides, tetracycline, and chloramphenicol

Bottom Line

- Listeria endocarditis is a fatal disease and if not treated promptly could lead to mortality (37-50%)

- Treatment options include:
  - PCN or ampicillin + gentamicin
  - If PCN allergy: vancomycin + gentamicin
  - Duration of therapy: 4-6 weeks

- Should be aggressive with treatment and monitor patient response to therapy
  - Clinical resolution of s&sx, drug levels for efficacy

- Best evidence → case reports & reviews!!!
Recommendations for Proper Food Handling by FSIS and CDC

- Do not drink raw (unpasteurized) milk or foods that contain unpasteurized milk
- Wash raw vegetables thoroughly before eating
- Keep the refrigerator at 40ºF (4.4ºC) or lower; freezer at 0ºF (-17.8ºC) or lower
- Use precooked, perishable, or ready-to-eat food as soon as possible
- Keep raw meat, fish, and poultry separate from other food that will not be cooked and from cooked foods and ready-to-eat foods
- Wash hands, knives, and cutting boards after handling uncooked food

Gelfand MS. Treatment and prognosis of Listeria monocytogenes infection. UpToDate Accessed April 27, 2007.
Recommendations for Proper Food Handling by FSIS and CDC

- Thoroughly cook raw food from animal sources to a safe internal temperature: ground beef 160ºF (71ºC); chicken 170ºF (77ºC); turkey 180ºF (82ºC); pork 160ºF (71ºC).

- The following additional recommendations were made for individuals at high risk such as pregnant women and those who are immunocompromised:
  - Do not eat hot dogs, luncheon meats, bologna, or other delicatessen meats unless they are reheated until steaming hot; avoid the use of the microwave oven since uneven cooking may occur.
  - Avoid getting fluids from hot dog packages on other foods, utensils, and food preparation surfaces; in addition, wash hands after handling hot dogs, luncheon meats, delicatessen meats, and raw meat, chicken, turkey, or seafood or their juices.
  - Do not eat salads made in the store such as ham salad, chicken salad, egg salad, tuna salad, or seafood salad.

Gelfand MS.  Treatment and prognosis of Listeria monocytogenes infection.  UpToDate Accessed April 27, 2007.
Recommendations for Proper Food Handling by FSIS and CDC

- Do not eat soft cheeses such as feta, Brie, and Camembert, blue-veined cheeses, or Mexican-style cheeses such as queso blanco, queso fresco, and Panela, unless they have labels that clearly state they are made from pasteurized milk.
- Do not eat refrigerated pates or meat spreads. Canned or shelf-stable products may be eaten.
- Do not eat refrigerated smoked seafood, unless it is contained in a cooked dish, such as a casserole. Refrigerated smoked seafood, such as salmon, trout, whitefish, cod, tuna or mackerel, is most often labelled as "nova-style," "lox," "kippered," "smoked," or "jerky." The fish is found in the refrigerator section or sold at deli counters of grocery stores and delicatessens. Canned or shelf-stable smoked seafood may be eaten.

Gelfand MS. Treatment and prognosis of Listeria monocytogenes infection. UpToDate Accessed April 27, 2007.