

INVASIVE PNEUMOCOCCAL PNEUMONIA: The Vancouver Downtown Eastside Outbreak



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Outline

- Downtown Eastside Outbreak
- *Streptococcus pneumoniae*
- Risk Factors
- Clinical Presentation
- Treatment
- Prevention
- Role of the Pharmacist
- Lessons Learned



Downtown Eastside Outbreak

Background 2006

- In BC
 - 427 cases of invasive pneumococcal disease (IPD)
(9.9 cases/100,000)
- In Vancouver
 - 161 (38%) cases (26.9 cases/100,000)
- *Streptococcus pneumoniae*
 - 140 serotype 5
 - Previously uncommon
 - In 2004 & 2005, 1 case per yr



Downtown Eastside Outbreak

August & September 2006

- St. Paul's Hospital (SPH)
 - Medical Microbiology Rounds
 - Review all positive blood cultures
 - Unusual cluster of IPD
 - 2 to 3 per wk (usually 0 to 5 per mo increasing in winter)
- Downtown Eastside (DTES)
 - ED admission & intubation in ICU
 - Hemodynamic support
 - Dialysis



Downtown Eastside Outbreak

October 2006

- Vancouver Coastal Public Health notified
- Isolates sent for serotyping at National Centre for Streptococcus in Edmonton
 - Serotype 5 identified in 2/3 of cases
 - Novel type in Vancouver
 - Previously 15 different serotypes
 - Shift in invasive pneumococcal isolates



Downtown Eastside Outbreak

November 2006

- 46 cases admitted at SPH
- Communicable Disease Control & Vancouver Community launched pneumococcal campaign with annual influenza program in DTES
 - Pneumococcal polysaccharide vaccine (23-valent includes serotype 5)
 - 6,000 immunized in 3 wk period
 - Target rooming houses, shelters, food banks, & other locations by outreach nurses
 - Modelled after campaigns for influenza, Hepatitis A/B
- Vaccination in ED for high-risk individuals



Downtown Eastside Outbreak

FREE BBQ


Tuesday, December 12
2:30–6 pm
Oppenheimer Park
400 Powell St. @ Cordova

Come to the park to take care of your stomach and get a shot to protect yourself against it too!
Enjoy a hot chocolate and the music of the March Band Band while you're waiting. Don't get in line, your free shot, enjoy a burger hot off the grill and a fresh salad.

WARNING

THERE'S A NEW BUG ON THE STREET THAT CAN MAKE YOU REALLY SICK, REALLY FAST.

Look for nurses in yellow jackets who can give you a shot to protect you.



Vancouver Coastal Health

Downtown Eastside Outbreak

December 2006

- 14 cases admitted to SPH
- 75% cases managed at SPH
 - Increase burden to wards & ICU; surgeries cancelled
- As of December
 - 131 isolates serotyped
 - 89 (68%) serotype 5
 - 31% required ICU admission

Vancouver Coastal Health

Downtown Eastside Outbreak

January 2007

- Number of cases declined

Vancouver Coastal Health

Downtown Eastside Outbreak

February 2007

- As of February 22
 - 151 cases serotype 5 (119 Vancouver)
 - 20 to 64 yrs (30 to 39 yrs)
 - 82% IPD risk
 - 70% pneumonia/bacteremia
 - 51% drug use
 - 37% hospitalization
 - 36% ICU
 - 24% homelessness
 - 21% Aboriginal
 - 8% (10) died

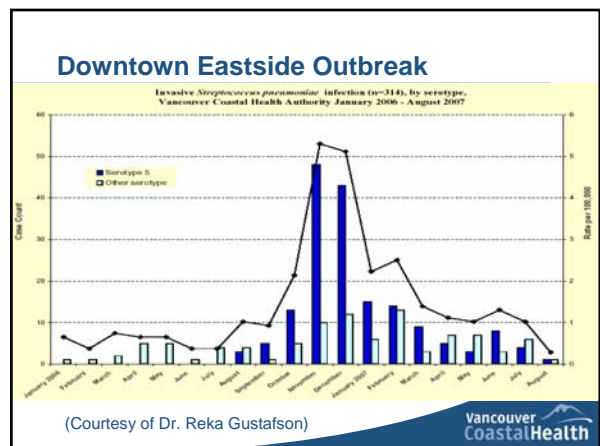
Vancouver Coastal Health

Downtown Eastside Outbreak

May 2007

- No cases for 3 to 4 wks
- Pneumococcal outbreak over

Vancouver Coastal Health



Downtown Eastside Outbreak

Rest of BC

- Serotype 5 cases admitted to other hospitals
 - 22 cases
 - 3 from Interior
 - 13 from Fraser
 - 2 from Richmond
 - 3 from Vancouver Island
 - 5 linked to inner city neighbourhood

Downtown Eastside Outbreak

Prevention programs

- Pneumococcal (23-valent) immunization of indigent & drug using people in adjacent regions
- Enhanced surveillance within BC
 - Local Public Health, BC Centre of Disease Control (Laboratory Services & Epidemiology Services), & National Centre for Streptococcus
- Stringent facility infection control

Downtown Eastside Outbreak

1. Largest outbreak of IPD in community
2. Rapid coordination & response by SPH, Public Health, & Vancouver Community
3. Outbreak controlled & limited to DTES

Streptococcus pneumoniae

(Curr Opin Crit Care 2006;12:470-476, Canadian Immunization Guide 2006, Cleveland Clinic J Med 2007;74:401-14)

- Gram-positive diplococcus with polysaccharide capsule
- Epidemiology
 - Leading cause of CAP, acute otitis media, meningitis, & bacteremia
 - In U.S., >500,000 pneumonia cases/yr
 - Up to 36% *S. pneumoniae*
 - Age specific incidence
 - <1 yr: 39.8 per 100,000 population/yr
 - 1 to 4 yrs: 24.6
 - ≥60 yrs: 13.3



Streptococcus pneumoniae

(Semin Respir Infect 1999;14(3):227-36, Microbiol Mol Biol Rev 2001;65:187-207)

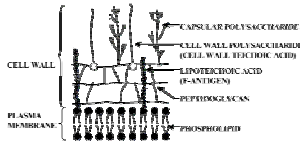
- Mortality rate
 - In U.S., 40,000/yr
 - 7 to 36%
 - Untreated bacteremic pneumococcal pneumonia
 - 80% case-fatality
 - Reduced to 20% with antimicrobial therapy
 - Associated factors
 - Elderly, comorbidities, PSI>90, severity of illness, antibiotic delay

Streptococcus pneumoniae

- Pathogenesis
 - Transmission via droplets
 - Nasopharyngeal colonization
 - Microaspiration
 - Infiltration, inflammation, & tissue damage

Streptococcus pneumoniae

- Serotypes
 - Over 90 capsular serotypes defined by chemical composition of capsule



Schematic of *S. pneumoniae* surface (modified: Musher 1995)

- Capsular polysaccharide acts as virulent factor
 - Protects from phagocytosis

Streptococcus pneumoniae

- Nasopharyngeal carriage in up to 40% of adults
 - At least one serotype
- Carriage provides immunity

Streptococcus pneumoniae

- Serotype 5
 - Previously uncommon in BC
 - 1 case/yr in 2004 & 2005
 - Responsible for recent outbreaks in Alberta
 - 0 to 3 cases/yr to 40 cases in 2005
 - 177 cases in December 2006
 - Pneumococcal polysaccharide vaccine program expanded to homeless, including hepatitis C
 - Manitoba & Saskatchewan also reported recent increases
 - Cluster in northern community

Streptococcus pneumoniae

- Invasive pneumococcal disease (IPD)
 - Infection of the bloodstream or cerebrospinal fluid by *Streptococcus pneumoniae*
 - Bacteremia in 10-20% cases
 - Increases mortality as compared to pneumonia alone
 - Susceptibility
 - Exposure to new serotype
 - Immunocompromise
 - Children & elderly, alcoholism, HIV
 - Chronic diseases
 - Cardiac, DM, pulmonary, liver, renal

Risk Factors

(Semin Respir Infect 1999;14:227-36, Int J Antimicrob Agent 2002;19:85-93)

- Extreme of ages
 - <5 yrs: daycare, smoke
 - >65 yrs: nursing home
- Populations
 - Alcoholic
 - Higher in blacks vs. whites
 - HIV (41 times higher)
 - Homeless
 - Institutionalized
 - IVDU
 - Smoker
- Comorbidities
 - Asplenia
 - Cirrhosis
 - CSF leak
 - DM
 - Heart or lung disease
 - Immunocompromise
 - Malignancies
 - Sickle cell disease
 - Cerebrovascular disease

Risk Factors

- DTES outbreak
 - Lived in or contact with DTES
 - 43 yrs mean age
 - 87% IPD risk factors
- Population
 - Homelessness
 - Rooming house
 - 77% smoked tobacco
 - **68% non-injection illicit drugs**
 - Smoked crack cocaine & other illicit drugs
- Comorbidities
 - Hepatitis C
 - HIV

Risk Factors

- Multivariate model
 - Alcohol use
 - Smoking
 - **Smoking of crack cocaine**
 - Vector of transfer?
 - Damage of airway?
 - Similar risk in TB
 - Drug use not associated



Risk Factors

- Why did an outbreak occur in DTES?
 - Serotype 5 introduced to DTES
 - Outbreak in homeless in Calgary
 - Naïve highly susceptible population
 - Risk factors
 - Alcoholism, chronic liver disease, homelessness, immunocompromise
 - RSV circulation, boiling water advisory, cold spell
 - Increase virulence of serotype 5
 - Increase morbidity not mortality

Clinical Presentation

- *Streptococcus pneumoniae* infections
(Semin Respir Infect 1999;14(3):227-36)
 - Otitis media
 - Sinusitis
 - Pneumonia
 - Meningitis
 - Complications
 - Respiratory failure
 - Empyema
 - Bacteremia (lobar consolidation)

Clinical Presentation

- DTES presentation
 - Pneumonia
 - Pericarditis
 - PID
 - Joint infection
 - Wound infection
 - 98% bacteremia
 - Many require ICU admission
 - 10 deaths

Clinical Presentation

- KL 55 yr M, 65 kg, admitted Sep 5, 2006
- **CC:** Respiratory distress
- **HPI:** Unwell x 3 d, SOB, cough, fever & chills. H/a & L-sided pleuritic chest pain x 2 d, emesis x 8
- **PMH:** COPD, HTN, PUD, EtOH, IVDU (cocaine, heroin), Hep B/C+, HIV-
- **MPTA:** Methadone, morphine, ramipril, rabeprazole
- **All:** Phenytoin
- **SHX:** DTES-no fixed address, unemployed, 3 beers/d, 1 ppd x 37 yr

Clinical Presentation

- On admission
 - T39.2°C HR110 BP131/82 RR24 O₂Sat70%
 - WBC 18.2 SCr 312 Alb 17
 - Sputum: 4+Poly, 3+GPC
 - Blood: Pending
 - CXR: LLL consolidation
 - Dx: Hypoxemic respiratory failure with septic shock
- Transfer to ICU

Clinical Presentation

- Clinical Course
 - Sep 5/6
 - Intubated & ventilated, on norepinephrine
 - Moxifloxacin 400 mg IV daily
 - Vancomycin 1250 mg IV x 1, then 1 g IV q12 h
 - Sep 7/8
 - Afebrile, wean to PSV, off norepinephrine
 - Self-extubated
 - Sputum: *S. pneumoniae* S – Pen, Moxi, Erythro, Doxy
 - Blood: *S. pneumoniae* S – Pen 0.023, Erythro, Vanco
 - D/C Vancomycin



Clinical Presentation

- Clinical Course
 - Sep 11
 - Transfer to CTU ward
 - Sep 13
 - Afebrile HR93 BP144/92 RR18 O₂Sat93%
 - AMA
 - Sep 18
 - Readmitted for partially treated pneumonia
 - AMA
- Total of 6 ICU d
- LOS 9 d



Clinical Presentation

- FL 49 yr F, 50 kg, admitted Dec 30, 2006
- CC: SOB
- HPI: Sudden onset cough x 2 d, nausea & hemoptysis x 1 d
- PMH: Asthma/COPD, chronic pain, cholecystectomy, cirrhosis (Hep B/C+), DM2, ESRD, HTN, MVR, nephropathy, pacer, pancreatitis
- MPTA: Amlodipine, ASA, domperidone, metoprolol, omeprazole, sevelamer, renavite
- All: Codeine
- SHx: DTES, opioid dependent, remote EtOH



Clinical Presentation

- On admission
 - T39°C HR125 BP122/80 RR40 O₂Sat96% on 2 L
 - A&Ox3
 - WBC 19.5 SCr 329 Alb 26
 - Sputum: 2+Poly, 2+GPC, 1+GNR
 - Blood: Pending
 - CT Chest: L hemithorax consolidation
 - Dx: Pneumonia with respiratory failure
- Admitted to respirology ward
- Transfer to ICU



Clinical Presentation

- Clinical Course
 - Dec 30
 - Intubated & ventilated
 - Ticarcillin/clavulanate 3.1 g IV q12 h
 - Vancomycin 1250 mg IV x 1
 - On norepinephrine
 - Jan 1
 - Sputum: 2+poly, 2+GPC, 1+GNR *S. pneumoniae* NRF
 - S – Pen, Moxi, Erythro, Doxy,
 - Blood 4/4: *S. pneumoniae*
 - S – Pen 0.016, Erythro, Vanco
 - D/C Ticarcillin/clavulanate
 - Penicillin 2 MU IV q4 h
 - PSV



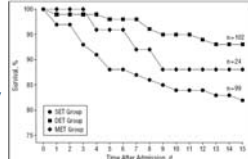
Clinical Presentation

- Clinical Course
 - Jan 6
 - Afebrile, WBC 10.7
 - Extubated
 - Transfer to ward
 - Jan 9
 - Discharge from hospital
- Total of 7 ICU d
- LOS 10 d



Treatment

- **Results:** Mortality SET significantly higher than DET
 - OR 3.0 (95%CI 1.2-7.6)
 - 18.2% SET vs. 6.9% DET (p=0.02)
 - Adjusted for predicted mortality
 - OR 6.4 (95%CI 1.9-21.7)



- **Conclusion:** Mono may be associated with significantly greater risk of death

Treatment

- **Limitations**
 - Retrospective
 - Excluded resistant strains
 - Timing of abx
 - Levofloxacin dose of 500 mg/d
 - Range of abx used
 - Change in abx not reported
 - Optimal duration
- Prospective, R, DB trial required in severe bacteremic pneumococcal CAP

Treatment

Martinez et al, 2003
(CID 2003;36:389-95)

- **Design:** R, Barcelona, Spain ('91-00)
- **Obj:** To assess if β -lactam + macrolide is associated with lower mortality in bacteremic pneumococcal CAP
- **Intervention:** β -lactam \pm abx vs. β -lactam + macro
- **Endpt:** Mortality
- **Results:** N=409 (171 (42%) β vs. 238 (58%) β /macro)
 - β : 62% 3rd ceph, 13% pen/aminopen, 11% 2nd ceph (36% abx)
 - β /macro: 82% 3rd ceph, 13% 2nd ceph, 68% erythro, 29% azithro

Treatment

- β : HIV, SCT, neutropenia, nosocomial, steroids, chemo, prior abx
- β /macro: Shock at presentation, ICU admission
- Mortality 9% (35/409)
 - 10% β vs. 8% β /macro (p=0.3)
 - Adjusted for shock: 0.4 (0.17-0.92, p=0.03)
- Prognostic factors for mortality
 - β (p=0.03), shock (p<0.0001), age \geq 65 yr (p=0.025), resistance (p=0.04)
- **Conclusion:** Addition of macrolide to β -lactam regimen may be associated with reduced mortality

Treatment

- **Limitations**
 - Retrospective
 - Not randomized
 - Change in practice over time
 - Differences in groups
 - β : Immunocompromised, 36% on other abx
 - β /macro: Shock & ICU
 - Effect only when adjusted for shock
- Interpret conclusion with caution

Treatment

- Baddour et al, 2003
(Am J Respir Crit Care Med 2004;170:440-4)
- **Design:** P, O, MC, International (98-00)
 - **Obj:** To assess if combo abx reduces mortality in pneumococcal bacteremia
 - **Intervention:** Mono abx culture vs. combo abx in 1st 2 d of blood
 - **Endpt:** 14-day mortality
 - **Results:** N=844 pneumococcal bacteremia
 - 592 for analysis of mono vs. combo
 - Mortality 16.5%
 - 11.5% mono vs. 10.4% combo (p=NS)

Treatment

- Critically ill (N=94)
 - 55.3% mono vs. 23.4% combo (p<0.01)
 - Mono: β -lactam most often
 - Combo: β -lactam/macrolide
- **Conclusion:** Combo abx may reduce mortality in critically ill
- **Limitations**
 - Not RCT
 - Not specific to pneumonia
 - Variable regimens
 - No definable regimen or duration
 - Combo effect only in critically ill pt
- Hypothesis generating

Treatment

Dwyer et al, 2006

(Eur J Clin Microbiol Infect Dis 2006;25:518-21)

- **Design:** R, Obs, MC (5 countries) ('93-95)
- **Obj:** To determine if β -lactam + macrolide combo is more favourable in bacteremic pneumococcal pneumonia
- **Intervention:** β -lactam vs. β -lactam + macro
- **Endpts:** Mortality
- **Results:** N=340 (75 β vs. 261 β /macro)
 - Mech ventilation: 7.7% vs. 16.5%
 - Mortality: 10.7% β vs. 19% β /macro, p=0.08
 - NS after APACHEII adjustments
- **Conclusion:** Requires further study

Treatment

- **Limitations**
 - Data from epidemiological trial
 - Previous study performed over 10 yrs ago
- Further prospective studies required

Treatment

Chokshi et al, 2007

(Eur J Clin Microbiol Infect Dis 2007;26:447-451)

- **Design:** Retro, Obs, Cohort, 2 Texas hospitals (JAN00-JUL03)
- **Obj:** To examine mono vs. combo tx on LOS & mortality in bacteremic *S. pneumoniae* pneumonia
- **Intervention:** Mono or combo abx in 1st 24 h of admission
- **Endpts:** LOS & mortality
- **Results:** N=108 (42 mono vs. 66 combo)
 - Mortality 16% (10% mono vs. 18% combo, p=0.3)
 - PSI IV/V: 25% mono vs. 31%, p=0.6
 - LOS 5.2 \pm 6.3 d mono vs. 9.1 \pm 9.5 d, p=0.05
- **Conclusion:** No differences in mortality, & increase LOS with combo

Treatment

- **Limitations**
 - Small sample size
 - Abx not standardized
 - Inability to follow tx resolution than LOS
- Further RCT for ideal CAP tx
- Conflicting data regarding use of combo, thus mono may be considered

Treatment

- **Combination vs. Mono therapy**

(Harbarth et al. CID 2007;44:87-93)

- **Combination**
 - May be beneficial in severe cases
 - Atypical pathogens in mixed infections
 - Immunomodulating effect
 - Bactericidal effect
 - Decreased resistance
- **Mono**
 - Pathogen-directed treatment
 - Narrow spectrum
 - Less adverse effects

Treatment

- Summary
 - Remains controversial
 - Retrospective/observational/non-randomized
 - Numerous confounders
 - No standardized abx
 - Timing of abx
 - Further studies
 - No definitive guidelines



Prevention

- Modify risk factors
 - Reducing exposure
 - Daycare, institution, smoke
 - Control medical conditions
 - COPD, CVD, diabetes, renal disease, smoking cessation
- Pneumococcal vaccine



Prevention

- Pneumococcal vaccine
(Vaccine 2004;2:2209-20)
 - Capsular polysaccharide highly immunogenic
 - Antibodies against polysaccharides protect against infection with homologous serotype
 - Reaction immature in young children
 - Polysaccharide vs. conjugate
 - Polysaccharide
 - Purified capsular polysaccharide antigens
 - Conjugate
 - Covalent binding to protein carrier (e.g. CRM197)



Prevention

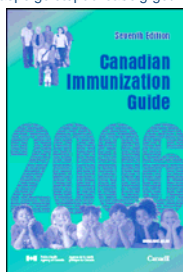
- Pneumococcal vaccine
(Vaccine 2004;2:2209-20, 2007;25:2194-2212)

	Polysaccharide 23-valent	Conjugate 7-valent
Serotypes	1,2,3,4,5,6B,7F,8,9N,9V,10A,11A,12F,14,15B,17F,18C,19A,19F,20,22F,23F,33F	4,6B,9V,14,18C,19F,23F
Coverage of pneumococcal diseases	85-90%	>85%
Age	>2 yrs to adults	<2 yrs
Immunogenicity	Low	High
Efficacy	50-80%	97.4%



Prevention

- Pneumococcal vaccine recommendations
(<http://www.phac-aspc.gc.ca/publicat/cig-gci/index-eng.php>)



Prevention

- Pneumococcal Polysaccharide 23-valent vaccine
 - Recommended usage
 - Ages
 - ≥5 yrs at IPD high risk
 - ≥65 yrs
 - Populations
 - Aboriginal
 - Alcoholism
 - HIV
 - Smoker
 - In BC
 - Crack cocaine use
 - Comorbidities
 - Asplenia
 - Cardiac, pulmonary, or renal
 - Cirrhosis
 - Cochlear implant
 - CSF leak
 - DM
 - Immunosuppression (Malignancies, SOT, steroids)
 - Sickle cell



Prevention

- Pneumococcal Polysaccharide 23-valent vaccine
 - Dose: 0.5 mL IM or SC
- Booster & re-immunization:
 - Routine re-immunization not recommended
 - For IPD high risk only
 - Anatomic or functional asplenia, cirrhosis, CRF or nephrotic syndrome, HIV, immunosuppression
 - One single re-immunization
 - After 5 yrs (if 1st dose >10 yrs) or
 - After 3 yrs (if 1st dose ≤10 yrs)
- Adverse reactions
 - Local soreness & erythema, fever

Prevention

- VGH Pneumococcal Vaccine Pre-printed Order

ASSESSMENT OF PNEUMOCOCCAL IMMUNIZATION ORDER		
CONTRAINDICATIONS to pneumococcal vaccine (check all that apply): <ul style="list-style-type: none"> <input type="checkbox"/> History of anaphylactic reaction to a previous dose of pneumococcal (23 valent) vaccine or its components; <input type="checkbox"/> Current febrile illness (greater than or equal to 38°C) (Reassess at a later date when afebrile); <input type="checkbox"/> HIV positive with CD4 count less than 100 cells/mm³ (Consult Medical Microbiologist to review patient). 		
ACTION: <ul style="list-style-type: none"> <input type="checkbox"/> Give: pneumococcal polysaccharide (23 valent) vaccine 0.5 mL SC or IM to the deltoid x 1 dose. To be given prior to discharge. (Fax order to Pharmacy.) Patient meets eligibility criteria and informed verbal consent obtained. "OR" <input type="checkbox"/> Do NOT give pneumococcal polysaccharide (23 valent) vaccine. (Do not fax order to Pharmacy. Leave in Physician's Orders.) <ul style="list-style-type: none"> <input type="checkbox"/> Patient meets eligibility criteria but refuses vaccine. <input type="checkbox"/> Patient does not meet eligibility criteria or vaccine is contraindicated. 		
Physician Signature _____	Physician Printed Name/PIC _____	Date/Time _____
5 years ago or longer		

Prevention

- Pneumococcal Conjugate 7-valent vaccine (Canadian Immunization Guide 2006)

Table 11. Summary Schedule for Pneumococcal Conjugate Vaccine in Previously Unvaccinated Children

Age at first dose	Primary series	Booster*
2-6 months**	3 doses, 2 months† apart	1 dose at 12 to 15 months of age
7 to 11 months	2 doses, at least 4 weeks apart	1 dose after 12 months of age
12 to 23 months	2 doses, 2 months apart	None
24-59 months		
Healthy children	1 dose	None
High-risk children	2 doses, 2 months apart	

* Booster doses to be given at least 2 months after the final dose of the primary series.
 ** Minimum age of 6 weeks
 † Minimum interval of 4 weeks

Role of the Pharmacist

- Awareness & heighten surveillance
 - Promed (<http://www.promedmail.org>)
- Multi-disciplinary team involvement
- Report unusual activity
- Be familiar with treatment guidelines
- Ensure availability of supplies
- Promote prevention strategies
- Vaccination of high-risk patients
- Educate patients

Lessons Learned

1. Largest community outbreak of IPD
2. Rapid coordination & response
3. *S. pneumoniae* remains important pathogen
4. Treatment with combination therapy is controversial
5. Prevention key strategy

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