Ensuring infections are correctly diagnosed before prescribing antibiotics

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Overview

• Predominantly hospital and adult medicine perspective

• I will not talk (much) about microbiological diagnostics!

• **Declarations:** Cubist, Pfizer, Astellas
Diagnosing infection the Osler way!

"Failure to examine the throat is a glaring sin of omission, especially in children. One finger in the throat and one in the rectum makes a good diagnostician."
pH1N1/09 case definition:

- Fever 38°C or history of fever
- and two or more of the following:
  - Cough
  - Sore throat
  - Headache
  - Rhinorrhea
  - Limb or joint pain
• PPV of definition = 0.38; NPV = 0.27
• 8 of 11 malaria cases would have been classified with flu’
• 3 of 8 with symptomatic flu’ would have been correctly diagnosed
• Some studies have shown clinical judgement to be as good as diagnostic definitions and molecular tests [Ann Emerg Med 2005;46:412-19; Br J Gen Pract 2001;51:630-634]

Table 2  Clinical features of symptomatic individuals following pathogen exposure.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Malaria infected (n = 11)</th>
<th>Influenza exposed(a) (n = 8)</th>
<th>(P) value(^b) (exposed)</th>
<th>Influenza infected(a) (n = 5)</th>
<th>(P) value(^b) (infected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>0</td>
<td>5</td>
<td>0.005</td>
<td>4</td>
<td>0.003</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>2</td>
<td>0</td>
<td>0.49</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Headache</td>
<td>10</td>
<td>6</td>
<td>0.55</td>
<td>4</td>
<td>1.0</td>
</tr>
<tr>
<td>Fever</td>
<td>8</td>
<td>2</td>
<td>0.18</td>
<td>2</td>
<td>0.55</td>
</tr>
<tr>
<td>Malaise</td>
<td>3</td>
<td>3</td>
<td>1.0</td>
<td>2</td>
<td>1.0</td>
</tr>
<tr>
<td>Myalgia/arthritis</td>
<td>10</td>
<td>5</td>
<td>0.72</td>
<td>3</td>
<td>0.21</td>
</tr>
<tr>
<td>Nasal symptoms</td>
<td>1</td>
<td>7</td>
<td>0.001</td>
<td>5</td>
<td>0.001</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>3</td>
<td>2</td>
<td>1.0</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Sore throat</td>
<td>0</td>
<td>3</td>
<td>0.058</td>
<td>3</td>
<td>0.018</td>
</tr>
<tr>
<td>Met case definition</td>
<td>8</td>
<td>3</td>
<td>0.18</td>
<td>3</td>
<td>1.0</td>
</tr>
</tbody>
</table>

\(a\) 8/11 influenza-exposed volunteers became symptomatic, 5/8 of whom developed viral culture-confirmed influenza infection.

\(b\) Analysis by two-tailed Fisher’s exact test versus malaria-infected volunteers.
Why do we need accurate early diagnoses?

59% vs 76% with a final diagnosis of CAP after (p<0.001); mostly non-infectious cardiac/pulmonary

66% vs 54% received antibiotics within 4 h of triage after (p<0.007)

Mean antibiotics utilized per patient increased from 1.39 to 1.66 (p<0.001)

Each 1 hour delay = 7.6% mean decrease in survival
What do we want from a clinical infection diagnosis?

<table>
<thead>
<tr>
<th>Component:</th>
<th>How?</th>
<th>Why?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ(s)/system(s) (Clinical)</td>
<td>History, examination, tests (CXR, WCC, CRP)</td>
<td>1) Causal pathogens are relatively predictable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2) Required intervention</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3) Prognostic</td>
</tr>
<tr>
<td>Microbiological</td>
<td>Diagnostics (Blood/urine culture, others) (Clinical assessment)</td>
<td>1) To avoid antibiotics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2) To target pathogen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3) Required intervention</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4) Prognostic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5) Epidemiology</td>
</tr>
<tr>
<td>Prognostic (severity)</td>
<td>Physiology Age, co-morbidity, etc. Clinical/microbiological diagnoses if available</td>
<td>1) Dictates level of intervention</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2) Discussion with patient and relatives</td>
</tr>
</tbody>
</table>
“A careful history will lead to the diagnosis 80% of the time?”
Won’t it?

In medical outpatients in patients referred by a GP, the history provided enough information to make 83% of diagnoses (N=80); 37 patients (46%) had a diagnosis that was the same as the referring GP.

BMJ 1975;2:486–9
The history *really* is important!

**Case 1**

- 31yo previously healthy female
- 5 day history of:
  - Fever
  - Myalgia
  - Lethargy
  - General malaise

**What’s the diagnosis?**
The history *really* is important!

Case 1

- 31yo previously healthy female
- Had competed in triathlon 6 days prior with swim in natural lake (UK)

- 5 day history of:
  - Fever
  - Myalgia
  - Lethargy
  - General malaise

What’s the diagnosis?
Examination is important too!

- 31yo previously healthy female
- Had competed in triathlon 6/7 prior with swim in natural lake
- 5 day history of:
  - Fever
  - Myalgia
  - Lethargy
  - General malaise

**O/E:** Febrile T>38°C  
“Possibly jaundiced”  
Pulse oximetry = 91% (air)

What’s the diagnosis?
So are we doing diagnosis well?

[Graph showing hospitalizations per 100,000 discharges for various conditions]

Hospitalizations for Which Certain Infection Codes Were Listed as a Primary Diagnosis, 2003–2011.

Data are from weighted national estimates from the Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS), Agency for Healthcare Research and Quality (AHRQ), based on data collected by individual states and provided to the AHRQ by the states.

Codes used: Sepsis/Septicemia (038.0–038.9, 785.52, 995.91–995.92), Pneumonia (480.0–480.9, 481, 482.0–482.9, 483.0–483.8, 484.1–484.8, 485, 486), Intra-abdominal Infection (008.45, 009.0–009.3, 540.0–540.9, 541, 542, 543.9, 562.01, 562.03, 562.11, 562.13, 567.0–567.9, 569.5, 569.61, 569.71, 569.83, 572.0–572.8, 574.00–574.91, 575.0–575.9, 576.0–576.9, 614.0–614.9), Urinary Tract Infection (590.00, 590.01, 590.10, 590.11, 590.2, 590.3, 590.80, 590.81, 590.9, 595.0, 595.2, 595.3, 595.4, 595.89, 595.9, 597.0, 597.80, 597.89, 598.00, 598.01, 599.0), and Bacteremia (790.7).
# How often is UTI really present?
## Snap-shot audit of patients on DME wards treated as UTI Nov. 2011

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>N = 25</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(16% of drug charts screened)</td>
</tr>
<tr>
<td>No culture sent</td>
<td>11 (44%)</td>
</tr>
<tr>
<td>No growth on MSU</td>
<td>7 (28%)</td>
</tr>
<tr>
<td>Mixed growth</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>1 bacteraemic</td>
<td></td>
</tr>
<tr>
<td>+ MSU for single organism</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>1 asymptomatic</td>
<td></td>
</tr>
</tbody>
</table>

**Clinical diagnosis UTI**

*Acknowledgement: Sean Ninan (ST3), Gurjit Chokkar (ST3), Wuthinan Nivatvongs (FY1), Damian Sweeney (FY1), DME, HEYHT*
### Reasons for delayed or inappropriate initial antibiotic therapy identified by post-implementation qualitative field-notes

(Note: Many patients had more than one reason for variance)  

<table>
<thead>
<tr>
<th>Reason</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrong initial diagnosis in the AMAU/A&amp;E</td>
<td>31</td>
</tr>
<tr>
<td>Failure to prescribe a stat dose</td>
<td>28</td>
</tr>
<tr>
<td>Seen late by the admitting doctor*</td>
<td>19</td>
</tr>
<tr>
<td>No clear reason identifiable</td>
<td>12</td>
</tr>
<tr>
<td>Stat dose prescribed, but delay in prescription or administration*</td>
<td>10</td>
</tr>
<tr>
<td>CXR not reviewed or acted on</td>
<td>6</td>
</tr>
</tbody>
</table>

Audit of investigations performed in 24 hours either side of blood cultures

<table>
<thead>
<tr>
<th>Investigation</th>
<th>% missing (N = 427)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBC</td>
<td>3%</td>
</tr>
<tr>
<td>BCP</td>
<td>3.5%</td>
</tr>
<tr>
<td>CRP</td>
<td>10.5%</td>
</tr>
<tr>
<td>Urine</td>
<td>70%</td>
</tr>
<tr>
<td>CXR</td>
<td>31%</td>
</tr>
</tbody>
</table>

- 23% had neither CXR nor urine
- 10% had “sepsis/PUO” on the request, but did not have a CXR or urine
- 19% of episodes had all 5 investigations performed

Acknowledgement: Wearmouth D, Thompson N
The history is really important!

Case 2

• 58yo male
• 15 units alcohol/day
• Admitted with
  – x1 episode haemoptysis
  – Productive cough 1 week with green sputum

• **O/E:** Febrile T>38°C

• What’s the diagnosis?
The history is really important!

Case 2

- 58yo male
- Worked in Brazil for last 15 years
- 15 units alcohol/day
- Admitted with
  - x1 episode haemoptysis
  - Productive cough 1 week with green sputum

- **O/E:** Febrile T>°C

- **What’s the diagnosis?**
Interpretation of tests is history dependent!

Case 2

• **CXR:**
What happened next

Case 2

• Diagnosed alcoholic liver disease
• Treated for community-acquired pneumonia
• Discharged home with plan for repeat CXR and follow-up at 6 weeks
• Readmitted 10 weeks later
Consequences

- Unnecessary exposure to 9d IV piperacillin-tazobactam and 5d IV clarithromycin
- Delayed diagnosis of true infection
- Death (disseminated TB)
What can we do when we can’t make a clear diagnosis quickly?

<table>
<thead>
<tr>
<th>Severity</th>
<th>Infection without SIRS</th>
<th>Sepsis (Infection + SIRS)</th>
<th>Severe sepsis or septic shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission decision</td>
<td>Clinical judgement</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Oxygen</td>
<td>Usually not required</td>
<td>Sometimes</td>
<td>Yes</td>
</tr>
<tr>
<td>IV fluids</td>
<td>Usually not required</td>
<td>Sometimes</td>
<td>Yes</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Await tests or narrow-spectrum oral therapy</td>
<td>Oral or IV, narrow or broad-spectrum depending on clinical judgement</td>
<td>IV, broad-spectrum (or narrow-spectrum if microbe known)</td>
</tr>
</tbody>
</table>

**Caveats:** suspected/proven meningitis, endocarditis, septic arthritis, osteomyelitis, abscess or clinical judgement overrules
Predicting mortality using severity scores in sepsis

Diagnostic and prognostic accuracy of clinical and laboratory parameters in community-acquired pneumonia

Beat Müller¹, Stephan Harbarth², Daiana Stolz³, Roland Bingisser⁴, Christian Mueller¹, Jörg Leuppi³, Charly Nusbaumer⁵, Michael Tamm³ and Miriam Christ-Crain*¹

- fever, cough, sputum, chest signs and dyspnoea = AUC 0.79
- + PCT = 0.88
- + hsCRP = 0.90
- + hsCRP and PCT = 0.92
**History**
- Age
- Co-morbidity
- Epidemiology

**Examination**
- Physiology

**Investigations** (non-microbiological)

**Pathogen**
- Identity
- Resistance
- MIC
- Virulence

**Biomarkers**
- CRP
- Procalcitonin
- The X Factor!

**Diagnosis**

**Prognosis**

**Level of intervention**
Conclusions

• We must do the basics of diagnosis well

• We must organise our health services so the basics can be done well

• Point-of-care diagnostics/prognostics absolutely needed, but must always interpret in context
To finish!

“The value of experience is not in seeing much, but in seeing wisely”

“In seeking absolute truth we aim at the unattainable and must be content with broken portions”