Cost-effectiveness and managing invasive candidiasis in the ICU

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Candidiasis is a problematic fungal infection

Treatment Costs $13,000

4/10 cases will die

Difficult to diagnose

- slow turnaround time
- symptoms hard to distinguish from other forms of sepsis

Incidence density rose 3.5 times in 10 years to 2008
Figure 1. Secular trends in incidence-density of candidaemia, Queensland 1999–2008. ■, all hospitals; □, adult tertiary hospitals; ▲, secondary hospitals; ○, community hospitals; ◆, paediatric tertiary hospitals.
Better outcomes arise from early initiation of anti-fungal therapy
   Fluconazole
   Caspofungin (for strains resistant to Fluconazole)

Problems with accurate diagnosis means prophylaxis might be attractive
Prophylaxis
Certain benefits now
Unknown future resistance costs

Conservative use of drugs
Uncertain benefits now
Less resistance in the future
Background

The Trade Off

Proportion treated in Current Period

Proportion effectively treated in Future Period
Antifungal treatment options prior to diagnosis of IC

- Empirical therapy (based on clinical features)
- Pre-emptive therapy (risk factors/candida colonisation)
- Prophylaxis (all pts on admission to ICU)

Putting patients into high risk & low risk groups can aid with treatment choices

Classification rules exist.....
Background

Six Classification Rules for high risk vs. Current standard of care (Baseline, 0.)

0. Baseline: No patients are in the high-risk group. Only empiric therapy is given to any patient not diagnosed with invasive candidiasis.

A. Clinical rule 1: either systemic antibiotic receipt on days 1-3 of ICU admission or central venous catheter on days 1-3, together with two additional risk factors described below. [25]

B. Clinical rule 2: either systemic antibiotic receipt on days 1-3 of ICU admission or central venous catheter on days 1-3, together with one other risk factor described below. [26]

C. Candida score: Candida score $\geq 2.5$. Candida score is: surgery (1 point); total parenteral nutrition (1 point); multi-focal Candida colonisation (1 point); severe sepsis (2 points). [27]

D. Colonisation index: $\geq 50\%$ of sampled superficial body sites are positive for Candida. [28]

E. Corrected Colonisation index: $\geq 40\%$ of sampled superficial body sites are positive (with 3+ growth) for Candida.) [28].

1. Universal: All patients are in the high-risk group so all patients receive antifungal prophylaxis.
To evaluate the change to costs and health benefits of using different classification rules (A – E & 1) to identify high risk patients.

Where Fluconazole prophylaxis treatment given to all patients in a high risk group.

This is a cost-effectiveness analysis
C = colonised

E = patients already receiving empirical Caspofungin treatment

I = Invasive Candidiasis (resistant and sensitive to Fluconazole)

A = discharged alive

D = died in ICU
Simulate with a Bayesian method
- number of cases in ICU
- total costs
- deaths & years of life lost

Classification rules (A to E, 1) used to populate low risk & high risk

Prophylaxis antifungal treatment given to patients in the high risk group
Data & Parameters

n = 6,750 non-neutropenic patients, June 2007 to Jan 2012

PAH, RBWH, Westmead, St Vincent’s Hospital, Concord Hospital, Nepean, RMH

Linked to 30,000 records on treatments with antibiotics and antifungal medicines

Assumed 10% of fluconazole patients developed resistance (Comert et al. Mycoses; 2006)

Swab data was also collected showing presence of Candidiasis on any of three sites (throat, perineum and urine)

Costing data synthesized from hospitals, PBS & expert opinion

Meta analysis used for treatment effectiveness & mortality relative risk
Systematic review and meta-analysis of antifungal agents for preventing fungal infections in liver transplant recipients

E. G. Playford · A. C. Webster · T. C. Sorrell · J. C. Craig
## Results

<table>
<thead>
<tr>
<th>Description</th>
<th>Rate</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>110/6750 with IC</td>
<td>1.75%</td>
<td></td>
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<tr>
<td>18/110 deaths</td>
<td>15.25%</td>
<td>IC cases</td>
</tr>
<tr>
<td>687/6750 deaths</td>
<td>10.2%</td>
<td>All patients</td>
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</tbody>
</table>

Relative risk of death with IC was 50% larger

816/6750 received empiric therapy under baseline (0)
Results

$64,000 per LYG

proportion resistant = 10%

Need to show uncertainty......
Life years difference * Willingness to pay – cost difference = Net Monetary Benefits
Results (as a linear measure) per 1,000 patients

<table>
<thead>
<tr>
<th></th>
<th>A vs 0</th>
<th>B vs 0</th>
<th>C vs 0</th>
<th>D vs 0</th>
<th>E vs 0</th>
<th>1 vs 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>cost difference ($1,000s)</td>
<td>19.91</td>
<td>3.54</td>
<td>-18.41</td>
<td>-32.28</td>
<td>-3.13</td>
<td>-20.57</td>
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<tr>
<td>life-years saved</td>
<td>0.47</td>
<td>0.39</td>
<td>0.19</td>
<td>-0.09</td>
<td>0.55</td>
<td>0.72</td>
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<tr>
<td>infections saved</td>
<td>2.57</td>
<td>2.60</td>
<td>2.68</td>
<td>0.16</td>
<td>2.45</td>
<td>7.12</td>
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<tr>
<td>deaths saved</td>
<td>0.32</td>
<td>0.23</td>
<td>0.22</td>
<td>-0.08</td>
<td>0.58</td>
<td>0.79</td>
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<tr>
<td>reduction in total ICU-days</td>
<td>7.18</td>
<td>10.42</td>
<td>10.91</td>
<td>8.94</td>
<td>6.68</td>
<td>23.01</td>
</tr>
<tr>
<td>reduction in infected ICU-days</td>
<td>63.50</td>
<td>61.76</td>
<td>39.47</td>
<td>5.11</td>
<td>35.08</td>
<td>103.34</td>
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<tr>
<td>NMB/patient $</td>
<td>10.14</td>
<td>21.45</td>
<td>30.81</td>
<td>26.68</td>
<td>38.54</td>
<td>66.97</td>
</tr>
</tbody>
</table>

Life years * Willingness to pay – cost difference = Net Monetary Benefits/pt.

0.47   $64,000  19,910   $10.14
Results (with uncertainty)

Net Monetary Benefit, wtp=$64,000
Results (scenarios)

Assumes that 1% & 50% of high risk patients receiving Fluconazole prophylaxis develop resistance.

Then treated by Caspofungin
Conclusions

Making every ICU admission high risk > universal Fluconazole prophylaxis (0) dominates all other approaches.

For 1000 admissions:

Saves 23 ICU-days, at $3,500 each

compensates the relatively low drug costs

Prevents most infections (7.12) and saves most life years (0.72)

This conclusion was robust to assumptions about resistance to Fluconazole emerging

A decision to treat all patients as high risk and so give all patients Fluconazole prophylaxis is cost-effective.