Trachomatous Scarring after the end of mass drug administration campaigns. Can we reduce the risk of new cases of Trichiasis?

Presenter: Matthew J. Burton

Author: Matthew J. Burton

Financial Disclosure

I have no financial interests or relationships to disclose.
Trachomatous Scarring after the end of mass drug administration campaigns.

Can we reduce the risk of new cases of trichiasis?

Matthew Burton
International Centre for Eye Health, LSHTM
The Natural History of Scarring Trachoma

What do we know?
## Incident / Progressive Scarring

<table>
<thead>
<tr>
<th>Progression factor</th>
<th>Sample size</th>
<th>Follow-up interval</th>
<th>Rate</th>
<th>Setting</th>
<th>Associated factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident conjunctival scarring (Wolle 2009)</td>
<td>367</td>
<td>5 years</td>
<td>20.4%</td>
<td>Tanzania</td>
<td>In children &lt;10yrs: Active disease/persistent infection Female gender Age</td>
</tr>
<tr>
<td>Incident conjunctival scarring (West 2001)</td>
<td>236 (age &lt;7yrs)</td>
<td>7 years</td>
<td>29.2% vs 9.6%</td>
<td>Tanzania</td>
<td>Higher rate was in children with severe-constant active disease Female gender Age</td>
</tr>
<tr>
<td>Worsening of conjunctival scarring (Wolle 2009)</td>
<td>85</td>
<td>5 years</td>
<td>47.1%</td>
<td>Tanzania</td>
<td>Not specified</td>
</tr>
<tr>
<td>Worsening of conjunctival scarring (Dawson 1990)</td>
<td>213†</td>
<td>14 years</td>
<td>68.5%</td>
<td>Tunisia</td>
<td>Active disease Household density</td>
</tr>
</tbody>
</table>
## Incident / Progressive Trichiasis

<table>
<thead>
<tr>
<th>Progression factor</th>
<th>Sample size</th>
<th>Follow-up interval</th>
<th>Rate</th>
<th>Setting</th>
<th>Associated factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>From conjunctival scarring to trichiasis (Munoz 1999)</td>
<td>523 (women)</td>
<td>7 years</td>
<td>9.2%</td>
<td>Tanzania</td>
<td>Active disease Chlamydial infection Increasing age</td>
</tr>
<tr>
<td>From conjunctival scarring to trichiasis (Bowman 2001)</td>
<td>297</td>
<td>12 years</td>
<td>6.4%</td>
<td>Gambia</td>
<td>Mandinka ethnicity</td>
</tr>
<tr>
<td>From conjunctival scarring to trichiasis (Burton 2006)</td>
<td>4898</td>
<td>5 years</td>
<td>3.2% - 15.1%</td>
<td>Tanzania</td>
<td>Increasing age</td>
</tr>
<tr>
<td>From minor to major trichiasis (Bowman 2002)</td>
<td>55</td>
<td>1 year</td>
<td>33%</td>
<td>Gambia</td>
<td>None mentioned</td>
</tr>
<tr>
<td>From minor to major trichiasis (Burton 2006)</td>
<td>75</td>
<td>4 years</td>
<td>37%</td>
<td>Gambia</td>
<td>Conjunctival inflammation</td>
</tr>
<tr>
<td>From unilateral to bilateral trichiasis (Bowman 2002)</td>
<td>46</td>
<td>1 year</td>
<td>46%</td>
<td>Gambia</td>
<td>Baseline pannus Hot ash as an aid to epilation</td>
</tr>
</tbody>
</table>
## Incident / Progressive Corneal Opacity

<table>
<thead>
<tr>
<th>Progression factor</th>
<th>Sample size</th>
<th>Follow-up interval</th>
<th>Rate</th>
<th>Setting</th>
<th>Associated factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>From conjunctival scarring +/- trichiasis to corneal scarring (Bowman 2001)</td>
<td>302</td>
<td>12 years</td>
<td>6.0%</td>
<td>Gambia</td>
<td>Baseline trichiasis</td>
</tr>
<tr>
<td>From trichiasis to corneal scarring (Burton 2006)</td>
<td>211</td>
<td>4 years</td>
<td>7.6%</td>
<td>Gambia</td>
<td>Increasing trichiasis severity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Conjunctival inflammation</td>
</tr>
<tr>
<td>From trichiasis to corneal opacity (Munoz 1997)</td>
<td>4898</td>
<td>10 years</td>
<td>27.2% - 53.5%</td>
<td>Tanzania</td>
<td>Increasing age</td>
</tr>
<tr>
<td>Worsening of corneal scarring (Bowman 2002)</td>
<td>96</td>
<td>1 year</td>
<td>34%</td>
<td>Gambia</td>
<td>Conjunctival inflammation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bacterial growth</td>
</tr>
</tbody>
</table>
What happens after community C. trachomatis infection is controlled?

- Very little long term data
- Need more data for sensible predictions...
- Probably slows down but TT still seems to develop
- Gambia
  - 5 year follow-up, 14 villages (Burton 2010)
  - single round of azithromycin
  - Very low infections levels
  - 2/456 incident TT cases
- Gambia
  - Programme did 400 cases during 2011
Why / How does trachoma progress?

(In the absence of *C. trachomatis*)
Pathway to Progression

- Stimulus
- Inflammation
- Scarring
Inflammation and Trachoma

• Chronic and Recurrent clinical inflammation are linked to progressive scarring (Dawson 1990, West 2001)

• Scarred conjunctiva is often inflamed in the absence of detectable *C. trachomatis*. (West 2005, Burton 2004, 2005)
Stimulus for Inflammation

- *C. trachomatis*
  - How much repeated exposure is needed to drive scarring?
  - How low does the prevalence of infection need to be?
  - Only limited direct data demonstrating the link between progressive scarring and ongoing *Ct* infection (Wolle 2009)

- Other bacteria

- Immunological?
Pathway to Progression

- Stimulus
- Inflammation
- Scarring
Innate Immune Responses

• Non-specific response
  • Epithelial cells
  • Immune system cells – Neutrophils / monocytes

• Pathogen pattern recognition receptors (TLRs)

• Release of chemokines / cytokines

• Inflammatory infiltrate response

• Increasing evidence of prominent innate immune responses in active and scarring trachoma (Natividad 2010, Burton 2011a, b, Hu 2012)

• Innate responses ↑ with bacterial infect. (Hu 2012)
Cell Mediated Immunity

• Specific responses to Ct antigens, resulting in a damaging inflammatory response

• Various possible mechanisms:
  • Delayed type hypersensitivity
  • Th2 response (IL13)

• Mixed / limited evidence from human studies
  • Protective
  • ? Pathological
Mechanisms for Scarring

- Stimulus
- Inflammation
- Scarring
Development of Scarring

- Chronic tissue damage (inflammation)
- Breakdown of extracellular matrix
- Matrix metalloproteinases (MMP)

- Fibroblasts
  - collagen production
  - ? Altered behaviour
  - ? Epithelial mesenchymal transformation
Many Questions Remain

- What happens to progression rates after Ct is controlled?
- Does repeated Ct infection modify the general responsiveness of the conjunctiva to other pathogens?
- Do other bacterial pathogens contribute to progressive scarring?
- Does EMT occur with a new population of conjunctival fibroblasts with altered behaviour?
Strategies to limit progressive scarring

- There is nothing directly proven
- Excellent long-term control of Ct in the population with implementation of “AFE”
- Reduce the conjunctival bacterial burden?
- Specific anti-MMP therapy?
Programmatic Implications

• Trichiasis is likely to continue to develop for many years after *C. trachomatous* has been controlled
• Programmes will need to maintain structures to detect and treat incident cases of trichiasis
• Empirical data is needed from regions where *Ct* has been controlled, to model the scale of this problem for program planning