

## Nullius in verba – Whom/What should we believe in GU Medicine?

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In September 2013, I was invited to talk at the first ‘Preventing Overdiagnosis’ conference, held at Dartmouth College in New Hampshire, USA. The meeting was organised by the British Medical Journal and the Dartmouth Institute for Health Policy and Clinical Practice. Mine was the only infectious disease presentation at the conference<sup>1</sup>, but the general message was not limited by subject matter or specialty. There was no commercial sponsorship and apart from those funded by their universities, the delegates had paid their own registration, travel and hotel expenses. Conflicts of interest (COI) were notable by their absence.

This lecture formed the basis of my presentation at the SLCV 19<sup>th</sup> Academic Sessions entitled ‘Overdiagnosis in Sexually transmitted Infections’ but the content of the talk ended up dealing more widely with conflict of interest (COI), a subject that I have returned to over the years in Colombo<sup>2</sup>.

### Overdiagnosis

In our practice of medicine we are bombarded with change, or ‘improvement’, in the diagnostic tests we use and in the very definitions of disease. We should all be suspicious of the motives behind those championing such changes. Screening for disease is particularly prone to manipulation by those with vested interests<sup>3</sup>.

Examples outside our specialty include the PSA test for prostate cancer, mammography for breast cancer and tests for depression, bone density and pulmonary embolism. Current definitions based on ‘estimated glomerular filtration rate’ (EGF) suggest that more than 50% of over 70s are suffering from ‘chronic

kidney disease’; it comes as no surprise to learn that nine of 16 members of the guidelines working party had ties with industry and that “*funding came from a consortium of pharmaceutical or device manufacturers*”<sup>4</sup>.

This widening of disease definition, seen also with hypertension and hypercholesterolaemia, along with new conditions like ‘pre-diabetes’, benefit commercial interests more than patients. Dr Kulasegaram gave a better HIV illustration than mine at the 2014 Sessions<sup>5</sup> pointing out the rise (WHO) in threshold for starting ARV from CD4 < 200 in 2002, via < 350 in 2008, to < 500 in 2013. The level of count at which to start treatment is, I am sure, based on sound clinical arguments but would convince me more were it not for the obvious benefit to the manufacturers of antiretroviral drugs.

There is no shortage of examples of overdiagnosis by screening in our own specialty: NAATs give false positives in gonorrhoea and I am suspicious of their use for chlamydia and other organisms, quite apart from problems with environmental contamination<sup>6</sup>. Herpes serology and misinterpretation of serological tests for syphilis add to the risk of overdiagnosis and overtreatment.

### Pelvic inflammatory Disease (PID)

The main thrust of my talk at Dartmouth College was the illogical and wasteful use of antigonococcal agents in the treatment of PID. I addressed this problem at the 17th Annual Sessions<sup>2</sup>. By happy irony, one month before my USA talk, the BMJ published a ‘Practice’ article on PID, aimed at GPs<sup>7</sup>. Apart from a dogmatic definition: “PID is due to

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infection in the upper genital tract...”, it quoted “the best recent data on easily missed PID comes from a retrospective audit...”, a research article with questionable methods (retrospective), results (did these patients have PID?), statistics (non-robust use of parametric tests on a skewed population) and conclusions (exactly opposite conclusions could have been drawn from the ‘data’)<sup>8</sup>. The article elicited three robust responses from your author<sup>9</sup>.

The recommendations<sup>10,11,12</sup> and prescription of anti-gonococcal therapy in PID are confounded by a combination of factors: a ‘shortage’ of gonorrhoea, confused definition and poor diagnosis. These matter since serious antimicrobial resistance threatens total loss of therapeutic options.

1. **‘Shortage’ of GC.** In many (if not most) populations, the incidence, and prevalence, of GC is low. Good figures are scarce but in the UK gonorrhoea is responsible for 1.7% of reported PID<sup>13</sup>. In Sweden the figure is 1.6%<sup>14</sup>. Rather like bacterial infection in sore throats, there is no indication to use antibiotics if a sensitive bacterium is unlikely to be present.

2. **Confused definition of PID.** In textbooks and guidelines the differential diagnosis of ‘PID’ is long and comprehensive, ranging from ectopic pregnancy, via UTI and PCO, to endometriosis. In the *clinical* setting, however, pelvic *inflammatory* disease is considered synonymous with pelvic *infective* disease.

3. **Poor diagnosis.** Symptoms and signs attributed to PID constitute pointers with very poor sensitivity and specificity. Further, the population of patients presenting to the venereologist, the gynaecologist, the general practitioner or the casualty department may be very different. Acute salpingitis with fever is rare in UK GUM practice, more common in gynaecology or A&E; in a university gynaecological practice, Bjarling could confirm only 59% of 208 clinically diagnosed PID at laparoscopy<sup>14</sup>. Were symptoms and signs put up for approval by the FDA

as a diagnostic test for PID, they would not ‘reach first base’.

In resource-rich countries, diagnosis (and exclusion) of gonorrhoea is almost exclusively by use of nucleic acid amplification tests (NAATs). In spite of their manufacturers’ claims, NAATs are not fool-proof<sup>15</sup>.

4. **Antimicrobial resistance (AMR).** The UK<sup>10</sup>, European<sup>11</sup> and N. American<sup>12</sup> guidelines all recommend the use of anti-gonococcal antibiotics (cephalosporins, usually ceftriaxone) in ‘undiagnosed’ PID, in spite of acknowledging the importance of non-infectious causes. Further, they all suggest empirical treatment for partners, in one case<sup>12</sup> “*regardless of the etiology of PID or pathogens isolated from the infected woman*” (my italics).

There have now been several reports of ceftriaxone treatment failures<sup>16</sup> and the WHO has produced a global action plan to control the speed and impact of antimicrobial resistance in *N.gonorrhoeae*<sup>17</sup>. We cannot afford to squander our last remaining weapon!

#### **Epidemiological treatment of gonorrhoea**

When faced with the management of PID and possible infection, there should be no delay in prescribing anti-*chlamydial* antibiotics, macrolides or tetracyclines (or certain fluoroquinolones) and there is an argument for treating partners epidemiologically. However, IT IS DIFFERENT WITH GONORRHOEA!

In a report of 604 cases of gonorrhoea in women<sup>18</sup> in 1976 (an era when diagnosis preceded treatment) we showed that epidemiological treatment would have identified only 4 of 16 GC-positive women who defaulted from follow-up, but would have unnecessarily diagnosed and treated 128 gonorrhoea-negative women (the number of contacts who would not have been infected<sup>19</sup>). A short time before that, the Americans, by dint of epidemiological, cluster, prophylactic and ‘post-hoc’ treatment of GIs in

South-east Asia had bred out the so-called 'Vietnam Rose', a strain with chromosomally-mediated reduced penicillin sensitivity, for which the average pair of buttocks could not accommodate the required dosage of penicillin.

### Importance of prevalence

I have used our own experience at St Thomas' Hospital to exemplify the hazards of indiscriminate use of inappropriate tests<sup>20</sup>. Our first DNA assay for gonorrhoea, used early in the Millennium, gave 375.9 false positives per 100,000 tests. Knowing the breakdown of gonorrhoea prevalence by gender, age-group and ethnicity for our local population, it was inevitable that the use of this test in white women over 30 years in age (gonorrhoea rate 4.7 per 100,000 per year<sup>20</sup>) would result in 98.8% of positives being false-positives. Point-of-care tests for a number of infections are becoming increasingly available, many using DNA or RNA amplification techniques. The importance of prevalence of disease in the tested population cannot be overstressed. If the prevalence is low, the likelihood of false positives is correspondingly increased. At last, in the Summer of 2014, the authorities in England recognised this fact in suggesting that with screening for gonorrhoea: "...below a prevalence of 1%, the majority of initial positive test results are likely to be false positives, suggesting unselected screening would be of limited public health benefit"<sup>21</sup>. This is an inevitable result of less than 100% specificity in the tests.

I applaud any move towards the 'old-fashioned' principle of diagnosis before treatment. Dr Andy Winter, in a plenary presentation<sup>22</sup> at IUSTI's Malta meeting, posed two important questions regarding PID: "What prevalence of gonorrhoea justifies routine addition of antigonococcal therapy?" and "What is the relative health outcome for immediate partner treatment vs. waiting for specific tests?" I addressed the potential problem of poor specificity in the previous paragraph; but, what of sensitivity? False negatives are of negligible importance in a low-

prevalence population and a recent model<sup>23</sup> has emphasized this, suggesting that the probability of a partner being infected ("*a conservative estimate*") with gonorrhoea or chlamydia is of the order of 0.4. Use of POCT would certainly reduce overtreatment of partners in these circumstances.

Management of possible chlamydial infection fares little better than for gonorrhoea: I quote Turner directly<sup>23</sup>: "*The study highlights that many symptomatic men and women currently receive treatment using an antibiotic primarily intended for treating chlamydia when this infection may not be present, and for which better treatments may be available.*"

### How reliable are tests and recommendations for other STIs?

The prevalence of genital infection with Herpes simplex II varies by gender, ethnicity and sexual orientation: gay men more than straight; women more than men; black more than white. As with all microorganisms, culture gives the definitive answer, if positive. With serology however we meet a familiar problem. A recent estimate<sup>24</sup> gave a figure of 4-5% for false positives. Adding this 4% to CDC's 2010 figure of 12% of adult whites with herpes II gives 25% (four of sixteen) of serological positives being actual negatives. A similar exercise on UK figures tells us that 33% of positives will actually be negative. Now you know why I never use serology in herpes.

We diagnose non-gonococcal, non-specific, urethritis by examining a sample obtained from the urethra under high-power microscopy. Important decisions are taken depending on the results of this hands-on POCT (for that is what it is). In the absence of routine culture or NAATs, epidemiological treatment of the partner of a man with NSU is standard practice. What variables influence this marriage-breaking diagnosis? The list is long and thought-provoking:

1. How long since last micturition?
2. Plastic or metal loop; or cotton swab?

3. How deep and vigorous the swabbing?
4. Transfer material to slide – ‘splat’ or ‘thick-and-thin film’?
5. Which bit(s) of slide to read?
6. How many fields?
7. Does anybody actually *count* polymorphs? Did they ever?

Jeremy Wilcox, 35 years ago, asked four experienced clinic slide-readers to assess 52 slides for possible urethritis and then gave them a further 52 slides<sup>25</sup>. What he didn't reveal was that the second set of slides was the same as the first but in a different order. They all used the same microscope and the results were both chastening and alarming: the comparisons *between* the four observers showed that the decision whether or not to treat differed in one-third of cases (36.5%). The *same* observer's therapeutic decision differed significantly in 16.8%. Remember that this exercise addressed only numbers 5 to 7 of the list above. I am not suggesting for a moment that you shouldn't call in the wife of the man with one-plus of pus cells for treatment but...

### Guidelines

Andy Winter, in his IUSTI plenary in Malta<sup>22</sup>, broke down the ‘statements’ in IUSTI Europe's published guidelines into three categories: ‘opinion’ (44%), ‘study’ (36%), and ‘RCT’ (20%). Only one in five guideline statements was backed up by data from a randomised controlled trial. The RCT contribution to guidelines varied from none (!) for Donovanosis to 10% in NGU, 14% in GC and 34% in PID. My reading shows that the only recent RCTs in the PID guidelines concern *Mycoplasma genitalium* and have no bearing on clinical decisions on whether to treat.

Guidelines can be useful, perhaps more so for the non-specialist who needs some dogmatic advice, but must be taken for what they are: guidelines, not laws. They are all fallible and I think, in our specialty at least (and with the possible exception of HIV

guidelines where all authors have potential conflicts of interest), that they are unlikely to be overly influenced by Pharma and Diagnostic companies.

### So what should we do?

I believe most people would benefit from a little more scepticism, not just in the relative value of diagnostic tests for STIs, but in life generally. In my 2014 lecture I reshewed a slide of recipes for horseradish sauce. Most people buy it rather than make it. *I make it* and the recipes from such sources as Eliza Acton, Mrs Beeton, Fanny Cradock and the Readers' Digest Cookbook, simply exhort you to “*grate the root and mix with condiments.*” I don't believe any of these authors had ever actually followed their own instructions. I prefer the Larousse Gastronomique's (English version) “*Wear rubber gloves and hold the root under water ... to reduce the irritation...*” Horseradish peroxidase is released when you grate this vicious root – I do so out of doors with the wind behind me. There is a non-culinary message here<sup>26</sup>.

I will summarise with a quote from a slide that I used in my presentation to the 2012 Academic Sessions<sup>2</sup>, ‘Lies, Damned lies and STItistics’:

*“The purpose of this talk is to make you all think when you see a figure, a statement, a calculation or a conclusion. Be suspicious, even if the source is a trusted senior Consultant from St Thomas”.*

\* *Nullius in verba*, (Latin for ‘take nobody's word for it’) is the motto of the Royal Society.

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