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Impact of DOTS compared with DOTS-plus on multidrug-resistant TB and TB deaths: decision analysis

Directly observed treatment strategy (DOTS) is an effective, often underused strategy for treating tuberculosis (TB), but may be insufficient for treating multidrug-resistant TB. The impact of the implementation of DOTS-plus in using toxic reserve drugs, known to be effective but costly, is unknown on overall TB control. This study set out to determine the impact of the World Health Organisation's DOTS with that of DOTS-plus on TB deaths in the developing world.

DOTS-plus involves the use of second-line antituberculosis drugs which are more toxic and expensive and less effective than first-line drugs. The regimen includes 2 or more drugs to which the isolate is susceptible, including 1 drug given parenterally for ≥ 6 months. Total duration of treatment is 18 - 24 months and treatment is directly observed.

The study was designed around decision analysis with Monte Carlo simulation of a Markov decision tree. The sources were people with smear-positive pulmonary TB.

Analyses modelled different levels of programme effectiveness of DOTS and DOTS-plus, and high (10%) and intermediate (3%) proportions of primary multidrug-resistant TB, while accounting for exogenous infection. The main outcome measure was the cumulative number of TB deaths per 100 000 of the population over 10 years.

In an area with 3% primary multidrug-resistant TB and under optimal implementation of the programme for 10 years, DOTS-plus would result in 1.5% fewer total deaths from TB than DOTS. This is because there would be fewer deaths from multidrug-resistant TB. So, optimal DOTS-plus would lower mortality from TB slightly, even in settings with low rates of multidrug-resistant TB. In an area with 10% primary multidrug-resistant TB and under ideal conditions, DOTS-plus would have a greater impact on lowering total mortality caused by TB and multidrug-resistant TB. In other words, DOTS-plus would have a greater impact in areas with higher rates of multidrug-resistant TB.

But, what is striking, is that if treatment of TB in the context of DOTS-plus is only 5% less effective than optimal DOTS, the cumulative number of TB deaths would be substantially higher under DOTS-plus than under DOTS alone.

So, the bottom line is that DOTS-plus would only be truly beneficial as a programme if it were truly 'plus' and did not divert resources from DOTS.

1. Sterling T, Lehman H, Friedman T. *BMJ* 2003; **326:** 574.

Crohn's disease or Crohn's diseases?

The opening line of this commentary in *Gut* is 'Disease behaviour in Crohn's disease is dynamic and not stable over time'. Commentators IDR Arnott and J Satsangi start at the beginning, with Crohn, Ginzburg and Oppenheimer's 1932 paper describing 'a disease of the terminal ileum, affecting mainly young adults and characterised by a subacute or chronic necrotising and cicatrising inflammation. The ulceration of the mucosa is accompanied by a disproportionate connective tissue reaction... which frequently leads to stenosis of the lumen of the intestine, associated with the formation of multiple fistulas.'

Over the years the term Crohn's disease has come into common usage. This covers a heterogeneous range of presentations, including the classic regional ileitis. There have been numerous attempts to subclassify Crohn's disease patients into subgroups

with similar, stable phenotypic characteristics. The driving force initially was to try to individualise therapy. Recently progress in the understanding of the molecular genetics of Crohn's disease and the need to relate genotype to disease phenotype have become an issue. Assigning disease phenotype may be difficult, but it is felt to be critical in determining the successful outcome of genetic association and linkage studies.

The Vienna classification of the working party of the World Congress of Gastroenterology proposed a subclassification of Crohn's disease according to three overriding phenotypic characteristics — age, location of disease and disease behaviour. It is the subclassification of disease behaviour into inflammatory (non-stricturing non-penetrating), stricturing (stenosing) and fistulating (penetrating) that has been seen as important recently.

A recent, large study shows that after 20 years, as many as 88% of the initial cohort studied had developed either stricturing (18%) or penetrating (70%) disease behaviour. Disease location was the most important factor identified in determining an alteration in disease behaviour. Small-bowel and anoperineal involvement predicted early stricturing and/or penetrating complications.

Other studies support the premise that Crohn's disease leads to stricturing and penetration in a substantial proportion of patients presenting with purely inflammatory disease.

In the index paper in *Gut*, Louis and colleagues[1] have looked in detail at factors which may influence the progression of disease behaviour. They examined 163 patients with an initial inflammatory phenotype and assessed changes in behaviour over 5 years. The changes were related to clinical characteristics, NOD2/CARD15 genotype and serological markers by univariate and multivariate analysis. They suggest, consistent with previous studies, that disease location is a critical determinant of disease progression and that smoking contributes to penetrating disease. The NOD2/CARD15 phenotype was not thought to be a determinant of disease, although familial disease distinguished stricturing and penetrating disease.

The major message from these studies is that disease behaviour is dynamic and not stable over time. Inflammatory disease is the commonest phenotype at presentation, and there appears to be an inexorable progression to either stricturing or penetrating disease over time. Approximately 25% of patients with inflammatory disease type at diagnosis will progress to penetrating disease over a 5-year period.

Progression may be inevitable, but what are the factors that influence the progression to either stricturing or penetrating disease?

Cigarette smoking is arguably the most important environmental factor identified in inflammatory bowel disease pathogenesis so far. In Crohn's disease, smoking not only increases disease susceptibility, but also has a well-documented detrimental effect on disease course, success of medical therapy, need for repeat surgery and overall mortality. Recent information even implicates smoking in Infliximab resistance. In the current study, the effect was seen even in relatively light smokers (1 cigarette per day). The mechanism is currently unknown, as is the relationship between smoking and progression to penetrating and not stricturing disease.

Anatomical location of disease is also strongly implicated in Louis *et al.*'s study. Patients with ileal disease tend to have stricturing disease, while those with colonic and perianal disease had penetrating complications.

How does genetics influence behaviour? The current study failed to identify an association between NOD2/CARD15 and disease behaviour. This contrasts with the three largest previously published studies which showed that carriage of one or more NOD2 allelic variants may protect against penetrating disease and predispose towards stricturing disease. Why is this? There are many possible explanations, including ethnic variation and phenotypic definitions. Louis *et al.* believe it is unclear whether the primary association of NOD2 genotype is with disease location or behaviour, or whether these are independent.

The influence of current therapies, immunosuppressants and novel biological treatments now used in Crohn's disease remains largely unknown.

The conclusion is that there is a great need for accurate subclassification of Crohn's disease. Disease behaviour is dynamic and needs to be viewed as a continuing process rather than as a snapshot.

1. Louis E, Michael V, Hugot JP *et al.* Early development of stricturing or penetrating pattern in Crohn's disease is influenced by disease location, number of flares and smoking, but not by NOD2/CARD15 genotype. *Gut* 2003; **53:** 552-557.