Letters

Triple therapy using two dosages of metronidazole along with amoxicillin and omeprazole to eradicate *Helicobacter pylori* infection: a randomized, open study

We report the findings of a prospective, randomized, open study on the efficacy of two different dosages of metronidazole along with amoxicillin and omeprazole in eradicating *Helicobacter pylori* infection in Iranian patients with duodenal ulcer or non-ulcer dyspepsia.

Forty-one patients (age range 25-65 years, median 42; 32 men) presenting to the Gastrointestinal Unit of Hospital Imam Khomeini, Tabriz, with a history of endoscopy proven duodenal ulcer (n=27) or dyspeptic symptoms and signs referable to the upper gastrointestinal tract with no ulcer at endoscopy (n=14) were included. At entry endoscopy was performed on each patient. Three biopsy specimens (for rapid urease test, microbiology, and pathological examination) were taken from the gastric antrum in all patients. Positivity of all tests was considered a prerequisite for inclusion in the trial. Patients provided written consent and Ethics Committee approval was obtained before conducting the trial.

Patients were randomized into two groups. Those in Group A (n=23) received 250 mg metronidazole every 8 hours, 1 g amoxicillin every 12 hours, and 20 mg omeprazole every 12 hours for 2 weeks; those in Group B (n=18) received 500 mg metronidazole every 8 hours, 1 g amoxicillin every 12 hours, and 20 mg omeprazole every 12 hours for 2 weeks. Endoscopy and gastric biopsy were repeated six weeks after starting drug therapy.

Eradication rates in patients in Groups A (65.2%, n=15/23) and B (83.8%, n=15/18) were significantly different ($p<0.001$). Eradication rates were similar in patients with or without ulcer. Drug side effects such as epigastric pain or metallic taste were more common ($p<0.001$) in patients in Group B (38.9% versus 13.1%).

Differences in eradication rates of *H. pylori* infection have been noticed with various drug regimens. The prevalence of metronidazole resistance among *H. pylori* strains has been considered as one of the factors to explain this difference.[1,2] This may be caused by the general use of metronidazole in developing countries for other infectious problems, such as protozoal diseases.[3] In the present study, two different dosages of metronidazole with amoxicillin and omeprazole were evaluated in patients with *H. pylori* infection. The results indicate that a higher dose of metronidazole (500 mg thrice daily) gives better eradication rates than 250 mg thrice daily in the Tabriz population.

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Determining the point of indifference – where costs of selective and universal immunization against hepatitis B are identical, in a cost-minimization exercise

Universal hepatitis B vaccination at birth is considered impractical in India, but vaccination along with DPT starting at 6 weeks (late vaccination) is considered more feasible. Late vaccination prevents horizontally acquired hepatitis B infection but not vertical spread. Vertical spread has been estimated to be responsible for 50% of carriers in India.[1] A program of testing all pregnant mothers and vaccinating at birth all babies born to hepatitis B-positive mothers (selective early vaccination) can block vertical spread but cannot prevent horizontal spread among the unvaccinated.

We describe how we calculated costs for the two strategies looking at the incidence of carrier state in a hospital in Delhi. For sensitivity testing we looked at how the cost-ratio for the two strategies changes as the incidence of carrier state changes. The carrier rate at which both strategies cost the same (point of cost indifference) is determined. We also look at how change in price of vaccine and price of testing affects the ratio. Finally, we show how this graph can be used to find the point of cost indifference, even in situations where the contribution to the carrier rate of vertical and horizontal transmission is not identical.

We tested the 6341 mothers who delivered at our hospital from 01.01.2000 to 31.12.2000 for hepatitis B status, using a method described by us earlier;[2] 52 of them (0.82%) were hepatitis B positive. The costs of various inputs are shown in the Table.

The Figure shows that the cost of universal immunization is two times more than the cost of testing all mothers and vaccinating the 52 babies born to hepatitis B carriers. The Figure also shows how the cost of selective immunization will change if hepatitis B carrier

Table: Cost of various components for vaccination by the two strategies (US$ 1 = Rs 50 for calculation)

Item	Cost for universal late vaccination (US $)	Cost for selective early vaccination
Vaccine cost per dose (sensitivity testing at Rs 20)	Rs 30 ($0.60)	Rs 30 ($0.60)
Consumables for vaccination	Rs 2 ($ 0.04)	Rs 2 ($ 0.04)
Hepatitis B test card (sensitivity testing at Rs 10)	Nil	Rs 30 ($0.60)
Consumables for performing test	Nil	Rs 6 ($0.12)
Cost in nursing time (assuming tests done area-by-area, of mothers pregnant >7 months)	Nil	Rs 10 ($0.20)
Additional expense for logistics and manpower to give first dose within 48 hours	Nil	Rs 20 ($0.40)
Additional cost for giving vaccine with EPI vaccines	Nil (all three doses)	Nil (second and third doses)

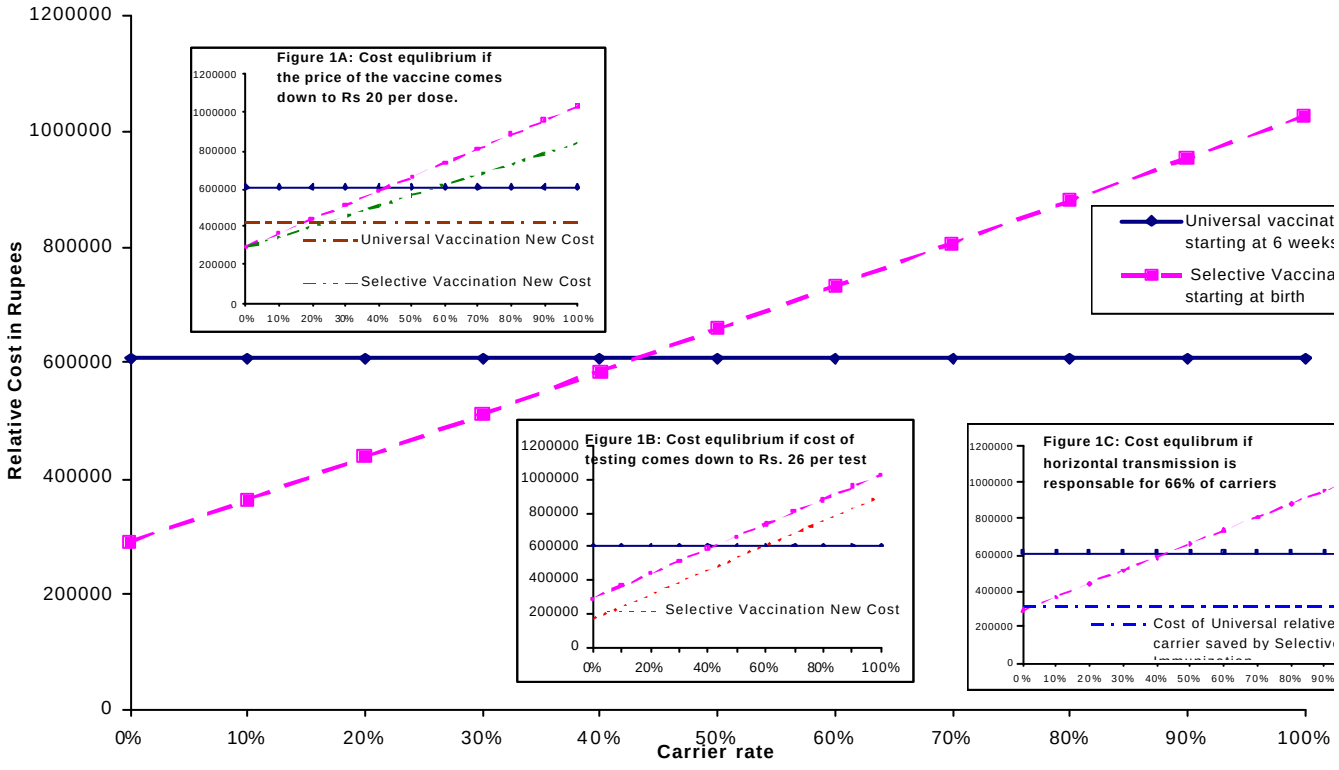
rate is higher.

The inset figures show how the interrelationship of the cost equation will change if one of the cost variables changes. If the cost of the vaccine decreases, the horizontal line representing cost of universal immunization will come down. Also, the slope of the cost for selective immunization will be less steep (Fig 1A). If the cost of testing comes down, the line showing cost of selective vaccination will start from a lower point on the Y axis (Fig 1B).

We found that 0.8% of mothers in our sample were hepatitis B carriers. Lodha *et al*[3] found the carrier rate in various studies from India to be between 0.6% and 4%. The graph lends itself to evaluating the relative costs of the two strategies at carrier rates from 0% to 100%.

Fig 1A shows that the point of cost indifference between universal and selective immunization is dependent heavily on the price of vaccine. We have done sensitivity testing with vaccine price at US$0.40 (Rs 20) per dose. In calculating costs, we have tried deliberately to underestimate costs of universal immunization by not adding cost of nursing time required for vaccination. Further, in the case of selective vaccination, we have estimated cost of testing with a higher mark up ($0.20; Rs 20 for nursing time per test), and factored in an additional cost of $0.40 (Rs 20) for giving the first dose of vaccine in the selective immunization group. In spite of this, universal immunization was two times more expensive than selective immunization. A previous study done by us, based on the Gross National Product (GNP) of the country, had shown that, for universal immunization to be cost effective in the country, the cost per dose of vaccine needs to come down to $0.122.[4] The present study shows that selective immunization is probably a more cost-efficient strategy for India.

Fig: Cost of universal and selective immunization at different carrier rates



In this cost-minimization calculation, horizontal and vertical transmission of hepatitis B is each considered as being responsible for 50% of the carriers. The same graphic method may be used to find the point of cost indifference, if it is assumed that horizontal transmission is responsible for 66% of the carrier state and vertical transmission is responsible for 33%. The graph showing cost of universal immunization can be redrawn at half the present cost, as this will be the relative cost per carrier saved, compared to carrier saved by selective vaccination (Fig 1C). The new cost-indifferent point can be re-estimated. Here universal immunization will be as cost-effective as selective immunization when the carrier rate is 1.1%. Similarly this point of cost indifference can be calculated for other ratios of horizontal to vertical transmission. The assumption, as in the rest of this paper, is that universal immunization starting at 6 weeks protects against all cases of horizontal transmission and selective immunization at birth protects against all cases of vertical transmission of hepatitis B.

Cost-minimization analysis is employed conventionally to compare costs when the effects of two interventions are identical.[5] The study shows how this cost-minimization can be used even when the contribution of vertical and horizontal transmission to the carrier rate is different (and when the benefits of the two strategies are not identical), after a process of scaling down costs of one intervention, to the level were benefits are comparable. Fig 1C encroaches into the territory of cost-effectiveness studies.

We believe the form of calculation we have adopted has not been utilized before. This novel application of cost-minimization can be used to determine the carrier rate where one strategy for immunization would be preferred over the other in a wide variety of conditions.

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Umbilical metastasis with squamous cell carcinoma of esophagus

Umbilical metastasis is usually seen with disseminated adenocarcinomas arising from intra-abdominal organs.[1]

A 65-year-old lady was diagnosed to have squamous cell carcinoma of lower third of esophagus. She received external radiotherapy and brachytherapy, following which she developed a stricture in the lower third of esophagus. She underwent metallic esophageal stent placement (*Ultraflex*, covered, 15 cm; Microvasive) with which her dysphagia improved and she gained 7 Kg weight over a 6 months period.

Two years later she noticed a small nodule in the umbilicus, which started discharging purulent offensive fluid. She also noticed significant anorexia and weight loss. On evaluation, she was pale, emaciated, and had a palpable hard lymph node in the left supraclavicular fossa. An infected swelling was noticed in the umbilical area (3 cm x 3 cm), which was hard, with no cough impulse (Fig). She also had hard nodular hepatomegaly (10 cm below costal margin). Rest of the systemic examination was unremarkable.

Chest X-ray revealed the stent in position. Upper GI endoscopy was suggestive of recurrence of malignancy at the lower end of esophagus. Fine-needle aspiration cytology from the umbilical nodule and supraclavicular lymph node revealed squamous cell carcinoma, similar in morphology to the esophageal lesion. Ultrasonography revealed hepatomegaly with multiple hypoechoic lesions suggestive of metastasis, along with multiple enlarged lymph nodes in the upper retroperitoneum and porta region. She was offered palliative therapy for pain, as she was not willing for any definitive therapy.

Umbilical metastasis accounts for 10% of lesions involving the anterior abdominal wall, and these are usually adenocarcinomas.[2] Clements stated that the finding of a metastatic nodule at the umbilical site almost certainly establishes the

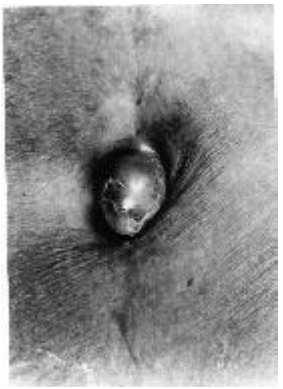

Fig: Ulcerated nodule in umbilicus