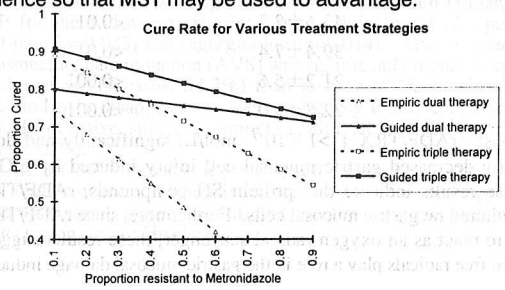
● RATIONALE FOR METRONIDAZOLE SENSITIVITY TESTING (MST) IN THE TREATMENT OF HELICOBACTER PYLORI INFECTION. A.J. DeCross, B.J. Marshall, R.W. McCallum, Dept. of Medicine, University of Virginia, Charlottesville, VA.

AIM is to examine the utility of the MST of Helicobacter pylori (Hp) in the development of better treatment strategies. **METHODS**: MST was done on Hp isolates of 166 patients not yet treated for Hp. The efficacy of dual therapy [metronidazole + bismuth subsalicylate, 2 wk, n=44] and triple therapy [tetracycline + dual therapy, 2 wk, n=20] was assessed for our metronidazole-sensitive and resistant Hp (MR-Hp). Efficacy rates of empiric and guided dual and triple therapy ("guided" by MST) were calculated against varying MR-Hp prevalence. In guided therapy, MR-Hp is treated with alternate therapy (e.g. tetracycline, bismuth subsalicylate, erythromycin and omeprazole, 2 wks) with a 70% efficacy rate. **RESULTS**: 35% of isolates were MR-Hp. Dual therapy eradicated 81.6% sensitive Hp and 16.7% MR-Hp ($p<.01$). Triple therapy eradicated 93.3% sensitive Hp and 80% MR-Hp ($p>.1$). In our calculations, triple therapy efficacy against MR-Hp was lowered to 50% (based on other reports). When the treatment efficacies are plotted against MR-Hp prevalence, several observations are made. At low MR-Hp prevalence, empiric triple therapy is the best choice; MST adds no benefit. At high MR-Hp prevalence, all guided therapy outperforms empiric therapy, and guided dual therapy performs as well as guided triple therapy. Guided dual therapy outperforms empiric triple therapy as the MR-Hp prevalence exceeds 40%. **CONCLUSION**: It is important to know the local MR-Hp prevalence so that MST may be used to advantage.



● TRANSCRIPTION ACTIVATION BY NON-METHYLATED AND METHYLATED HUMAN PEPSINOGEN PROMOTERS: DIFFERENCES IN DNA-PROTEIN INTERACTIONS. J.Defize, A. Timmerman and G. Pals. Institute of Human Genetics, Free University Amsterdam and RIVM, Bilthoven, The Netherlands.

Binding of nuclear protein factors to gene promoter regions as well as methylation of DNA are factors known to regulate gene expression. Recently, we have shown that in vitro CpG methylation at the HhaI site of a human pepsinogen A (hPGA) gene promoter region, greatly reduces expression of the reporter gene (1). However, deletion of the region encompassing this site had no effect on expression, indicating that the methylated site is capable of binding a repressive factor. We have therefore studied differences in DNA-protein binding between methylated and non-methylated DNA fragments in a gel shift assay. The effect of HhaI methylation on transcription was studied using different hPGA promoters, characterized by presence or absence of a stretch of 130 bp adjacent at the 3'end of the HhaI site.
A 72 bp fragment of the hPGA promoter, containing the HhaI site was amplified by PCR and methylated at GC^{m}GC with HhaI methylase;. Methylated and non-methylated fragments were endlabeled with ^{32}P and incubated with HeLa nuclear extracts. Unbound DNA and DNA-protein complexes were separated on PAGE and visualized by autoradiography. Transcriptional activity of hPGA promoters was studied in a transient expression assay, using monkey chief cells and CAT as reporter gene (1).
Results: PAGE of DNA fragments incubated with HeLa nuclear extracts reveals the presence of DNA-protein complexes for the methylated fragment, but not for the non-methylated fragment. At least two discrete complexes can be distinguished. Furthermore, methylation at the HhaI site in hPGA promoters containing the 130 bp insert has no effect on transcription, in contrast to promoters missing this insert, where HhaI methylation results in a 50-70% reduction in expression of the CAT gene.
Discussion: Methylation of a specific hPGA promoter sequence leads to differences in the forming of DNA-protein complexes. Moreover, the 130 bp insert abolishes the inhibitory effect of HhaI methylation on transcription, either by disrupting the protein binding site, or by moving the HhaI site further away from the transcription initiation site. These results indicate that the region around the HhaI site contains an important regulatory element. Absence of this region does not influence transcription and we therefore postulate that methylation of this site is required for binding of a putative repressive protein factor.
1. Defize J, Meijerink P, Bebelman JP et al. Gastroenterology 1992;102:A57.
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OMEPRAZOLE TREATMENT OF SEVERE ESOPHAGITIS IN CHILDREN

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In adults omeprazole has been demonstrated to be an effective treatment of severe esophagitis. In children there is no available study. We treated with omeprazole 11 children (6 males, median age 6 years 1 month; range 3 years - 11 years 2 months): 6 children with a body weight lower than 30 kg were treated with a daily dose of 20 mg and 5 children weighting more than 30 kg with a daily dose of 40 mg. Endoscopy and 24 hours pH-metry have been performed at diagnosis and after a mean of 3 months of omeprazole treatment. Follow-up endoscopy showed healing of esophagitis in 10 of 11 patients and persistence of esophagitis in 1 child belonging to the 20 mg group. This child healed when the daily dose was increased to 40 mg. Omeprazole decreased the median percentages of total pH<4 time from 14.6 to 2.4 (Wilcoxon-0.002), of postprandial pH<4 time from 13.2 to 2.5 (0.004), and of fasting pH < 4 time from 17.3 to 1 (0.002). In conclusion, omeprazole is an effective treatment of erosive esophagitis in children. In the treatment of esophagitis in children the optimal daily dose of the drug has not been determined yet, however, according to our data the 20 mg dose might not be sufficient.

SEROEPIDEMIOLOGY OF HELICOBACTER PYLORI (Hp) IN MEXICO.

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Hp is the etiologic agent of type B gastritis, which can progress to atrophic gastritis and eventually to gastric carcinoma (G.CA.). Distribution of the infection is worldwide. Higher prevalences have been described in Hispanics and in lower socioeconomical level, populations in which prevalence of G.CA. is also higher. México has clearly defined populations with different prevalences for G.CA. In order to investigate Hp infection in adults, we determined the presence and titers of IgG anti-Hp (Pylori-Stat, Wittaker Bioproducts, Walkersville, MD) in 210 serum samples of voluntary blood donors from 7 states in Mexico (30 donors/state). Titers of >1 were considered positive. Differences in seropositivity and anti-Hp titers were analysed according to state, age, gender and residency. In all individuals anti-Hp titers and age were correlated and prevalence of seropositive individuals were compared in three age groups (<29, 30-40, >50 years). Statistical analyses were done using Chi square, variance and Pearson r.

RESULTS:

States	Age(years) X ± 1ds	Sex M:F	Residency urban-rural	Anti-Hp IgG + (%)	Titers(X)	G.CA. (per10^5)
Chiapas	31 ± 8	28:2	4-26	28 (93)	2.2	6.8
Mexico	32 11	26:4	10-20	17 (57)	1.4	3.0
Michoacán	26 7	29:1	14-16	16 (53)	1.2	5.7
Morelos	35 8	28:2	12-13	22 (73)	1.7	5.8
Nvo. León	31 8	29:1	26- 4	19 (63)	1.9	5.0
Querétaro	30 8	22:8	12-18	15 (50)	1.1	3.8
Yucatán	32 7	28:2	15-15	19 (63)	1.2	7.4

Both prevalence and titers were different between the states ($p<0.01$). An association of 65% was found when anti-Hp prevalences were correlated to death rates due to G.CA. There were no differences in the distribution according to age, gender or residency nor was there a correlation between age and titers. Seropositivity was different in the three age groups studied (52, 72 and 74% respectively).
CONCLUSIONS. Prevalence of seropositivity was similar(65%) to that reported in the literature. Populations with higher seropositivity were those with a high death rate due to G.CA. The presence of high positivity rates in apparently normal individuals makes the interpretation of such results questionable.