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**Maestría y Doctorado en Ciencias Médicas, Odontológicas y de la Salud**

INSTITUTO NACIONAL DE CIENCIAS MÉDICAS Y NUTRICIÓN
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***Efecto de la administración profiláctica del Ciprofloxacino en la incidencia de infecciones graves y evolución de las citocinas pro- y anti-inflamatorias en pacientes cirróticos: Estudio aleatorizado doblemente a ciegas***

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## Contenido

**Título**

***Efecto de la administración profiláctica del Ciprofloxacino en la incidencia de infecciones graves y evolución de las citocinas pro- y anti-inflamatorias en pacientes cirróticos: Estudio aleatorizado doblemente a ciegas***

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**Resumen**

**Introducción y objetivo:** Existe poca información acerca de la profilaxis primaria en pacientes cirróticos. El objetivo del estudio fue evaluar la eficacia de la ciprofloxacina en la profilaxis primaria para infecciones bacterianas en pacientes con cirrosis y ascitis. **Material y Métodos**: Se realizó un estudio aleatorizado, doble ciego, controlado con placebo. Los pacientes se aleatorizaron a recibir ciprofloxacina 500 mg/día o placebo por un mes. Se realizó una evaluación basal, a la semana 4, 6, 12, 18 y 24, o en cualquier momento que ocurriera un evento de desenlace. **Análisis estadístico:** se calculó la probabilidad de mantenerse libre de infecciones bacterianas por medio de curvas de Kaplan-Meier y comparados con la prueba de log-rank. **Resultados:** se aleatorizaron 95 pacientes. En el grupo de ciprofloxacina 49 (51.6%) y en el grupo de placebo 46 (48.4%). 16 (32.7%) pacientes en el grupo de ciprofloxacina desarrollaron una complicación infecciosa y 13 (28.3%) en el grupo de placebo (P = NS). La probabilidad de mantenerse libre de infecciones bacterianas no alcanzó significancia estadística (P = 0.38). La probabilidad de supervivencia a las 24 semanas fue de 91% en el grupo placebo y de 98% en el grupo de ciprofloxacina (P = 0.28). La reducción del riesgo absoluto fue de 5%, la reducción del riesgo relativo fue de 6% y el número necesario a tratar fue de 20 pacientes. **Conclusión:** la profilaxis primaria con ciprofloxacina en pacientes cirróticos con ascitis quienes no tienen una indicación actualmente aceptada no mostró un efecto preventivo en el desarrollo de infecciones

bacterianas; aunque la administración de ciprofloxacina parece disminuir el riesgo de mortalidad.

## Introducción

Las infecciones bacterianas representan del 30-50% de las admisiones hospitalarias entre los pacientes con cirrosis hepática y tienen una mortalidad hasta del 50% (1,2). Lo anterior a pesar de que se ha logrado importante progreso en el tratamiento y profilaxis de la peritonitis bacteriana espontánea (PBE) en los últimos años (3-9). Hasta ahora, la profilaxis secundaria ha sido recomendada para pacientes con episodios previos de PBE debido al alto riesgo de recurrencia y muerte (32-70%) a un año de seguimiento (3, 10-12). En un meta-análisis reciente se observó que la profilaxis con antibióticos en pacientes cirróticos con sangrado gastrointestinal reduce la tasa de infección y mejora la tasa de supervivencia (13). Contrario a los datos anteriores, existe poca información en relación con la profilaxis primaria y hasta el momento el único factor de riesgo aceptado para el desarrollo de PBE en este grupo de pacientes es la concentración baja (< 1.5 g/dL) de proteínas en el líquido de ascitis (4, 14, 15).

La evidencia de que otras infecciones además de la PBE, juegan un papel importante en la morbilidad y mortalidad de los pacientes cirróticos ha ido en aumento (2, 16, 17). En una revisión sistemática (2), la mortalidad de pacientes cirróticos sin infección fue de 13.6% (18 cohortes, 2317 pacientes) comparado con una mortalidad del 40% en pacientes con alguna infección. La razón de momios para mortalidad en pacientes con infección fue de 3.75 (IC95%: 2.12-4.23). A

pesar de estos datos, hasta ahora todos los estudios se han enfocado específicamente en la profilaxis para PBE. El principal mecanismo involucrado en el desarrollo de infecciones bacterianas en cirróticos es la traslocación bacteriana. Tomando en cuenta que la presencia de ascitis es un marcador de descompensación de la cirrosis y a la traslocación bacteriana como el principal factor asociado al desarrollo de infecciones, es posible que todos los pacientes con ascitis, independientemente de otras complicaciones, se pudieran beneficiar con el uso de profilaxis primaria.

El objetivo del presente estudio fue evaluar la eficacia de la ciprofloxacina oral como profilaxis primaria de infecciones bacterianas en pacientes cirróticos con ascitis sin una indicación de profilaxis primaria actualmente aceptada. De manera secundaria, las concentraciones basales de las citocinas pro-inflamatorias y anti-inflamatorias fueron determinadas y evaluadas después de la administración de ciprofloxacina.

**Material y Métodos**

Se realizó un estudio aleatorizado, doblemente a ciegas controlado con placebo. El protocolo del estudio fue aprobado por el Comité Institucional de ética de Investigación en Humanos y registrado en la base ClinicalTrials.gov con el número NCT00760032. Se incluyeron pacientes mayores de 18 años de edad que otorgaran su consentimiento informado.

**Pacientes**

Ciento setenta y siete pacientes con cirrosis y ascitis fueron evaluados de abril/2008 a noviembre de 2009. El diagnóstico de cirrosis se realizó con base en datos clínicos, de laboratorio, ultrasonido y/o evidencia histológica. Los pacientes con etiología autoinmune de la cirrosis, historia de PBE, sangrado gastrointestinal activo, proteínas totales en líquido de ascitis <1.5 g/dL, uso de antibióticos en los 30 días previos, embarazo, encefalopatía ≥ grade 2, comorbilidades autoinmunes, tratamientos inmunosupresores, hepatocarcinoma u otros cánceres, alergia a las quinolonas y la presencia de infecciones bacterianas.

Los pacientes elegibles fueron aleatorizados a recibir ciprofloxacina oral 500 mg/día (Ciproflox, Laboratorios Senosiain, S.A. de C.V., México) o 500 mg/día de un placebo de apariencia idéntica por espacio de 1 mes, la apariencia de las cápsulas de ciprofloxacina y placebo era igual y fueron empaquetados en contenedores indistinguibles. Una secuencia aleatoria fue generada por computadora y se mantuvo sellada hasta que ocurriera un desenlace, un evento adverso o bien, al final del estudio. Los contenedores fueron numerados de manera consecutiva y asignados a los pacientes de la misma manera. Al momento de la inclusión, se les realizó a los pacientes una historia clínica completa con interrogatorio y exploración física, estudios de laboratorio (pruebas de función hepática, química sanguínea, biometría hemática y tiempos de coagulación, examen general de orina y placa de tórax). Se realizó la misma evaluación a la semana 4, 6, 12, 18 y 24 posteriores o en cualquier momento que ocurriera un desenlace. Los pacientes incluidos continuaron con sus medicamentos de base durante el tiempo que permanecieron en el estudio. El apego al medicamento del

estudio se realizó por medio de la cuenta de cápsulas al final del periodo de 4 semanas de tratamiento. Los pacientes que no tomaron los medicamentos del estudio por al menos dos semanas fueron considerados como no apegados al tratamiento y fueron eliminados del análisis por protocolo. Los medicamentos del estudio fueron suspendidos cuando ocurrió un desenlace. Los pacientes con encefalopatía secundaria a transgresión de la dieta, estreñimiento o al uso de diuréticos continuaron en el estudio bajo ajuste del tratamiento.

Infección, sangrado gastrointestinal, encefalopatía hepática, eventos adversos graves o muerte fueron los desenlaces de interés. Se sospechó de infección cuando se documentó fiebre, dolor abdominal, síntomas urinarios o respiratorios. Peritonitis bacteriana espontánea se definió como una cuenta ≥ 250 PMN $mm^3$ en la muestra de ascitis (18, 19). Infección de vías urinarias se diagnóstico en los casos con disuria, poliaquiuria, urgencia vesical, dolor lumbar y/o fiebre y que confirmaron por medio de un cultivo de orina (20,21). Se diagnosticó infección de vías respiratorias bajas cuando se documentaron rudeza respiratoria, estertores, infiltrados en la placa de tórax y se acompañaron de al menos 2 de los siguientes datos: fiebre o hipotermia, diaforesis, tos seca o con expectoración, dolor torácico o disnea (22). Si no se documentaron infiltrados en la placa de tórax se consideró como infección de vías respiratorias altas. Bacteremia espontánea se consideró a un evento de respuesta inflamatoria sistémica en un paciente dado, en el cual existió aislamiento de algún microrganismo en cultivos de sangre sin documentarse un foco infeccioso primario (23). Se catalogaron como graves aquellas infecciones que requirieron de hospitalización para su tratamiento.

Cuando ocurrió cualquiera de los desenlaces se consideró como falla e implicó la interrupción de la toma del medicamento del estudio y la administración del tratamiento estándar para cada condición de cada paciente.

**Métodos**

Se tomaron 20 ml de sangre periférica en tubos heparinizados libres de pirógenos (Becton Dickinson, Mississauga, Ontario, Ca).

*Determinación de lipopolisacárido (LPS) plasmático:*

La endotoxina plasmática se determinó utilizando el ensayo cromogénico cuantitativo del lisado del limulus del amebocito (LAL), QCL-1000 (Biowhitakker, Inc, Walkersville, MD, USA) acorde con las instrucciones del proveedor: los inhibidores de la endotoxina se eliminaron diluyendo el plasma 1:10 con agua libre de pirógenos, y calentando las muestras a 70°C durante 5 minutos. Se ajustó el pH de las muestras en un rango de 7-8, por medio del uso de soluciones de hidróxido de sodio 0.1N y ácido clorhídrico 0.1N. En una microplaca estéril, se colocaron los estándares (7 estándares preparados de una solución stock de endotoxina de *E. coli* proporcionada por Biowhitakker), el blanco y las muestras por duplicado. Se adicionó el LAL y se incubó la placa por 10 minutos. Se adicionó el sustrato cromogénico (precalentado a 37±1.0 °C) y se incubó la placa por 6 minutos. Finalmente, se adicionó ácido acético glacial al 25% para interrumpir la reacción. La reacción se llevó a cabo a 37±1.0 °C. Se leyeron las densidades ópticas en el lector de microplaca a una longitud de onda de 405-410 nm.

*Determinación de secreción de TNFalfa y citocinas:*

La secreción de TNF$\alpha$, IL-1, IL-6, IL-10, e IL-12 se determinó por medio de paquetes comerciales de ELISA (OptEIA$^{TM}$, BD Pharmingen, San Diego, CA, USA) de acuerdo con las instrucciones del fabricante. Los límites de detección fueron 4 pg/mL para TNF, IL-1β, IL-6, and IL-10, y de 15 pg/mL para IL-12. Para cada paciente cada prueba fue hecha por duplicado. Las microceldas de poliestireno estuvieron cubiertas por un anticuerpo monoclonal específico contra cada una de estas citocinas. Se agregó medio de cultivo o bien las soluciones estándar de citocinas y se incubó por tres horas (aproximadamente). Se adicionó un segundo anticuerpo policlonal específico. Finalmente, se agregó una solución cromogénica. El color se provocó por la reacción de un conjugado. La absorbancia se medió a 450 nm y las concentraciones (pg/ml) de citocinas se obtuvieron con base a la curva estándar.

***Análisis Estadístico***

El tamaño de la muestra fue calculado asumiendo una diferencia de 25% en la incidencia de infecciones entre los grupos (4, 6-8). Para detectar esta diferencia a un nivel de significancia (una sola cola) de 5% y un poder de 80%, se obtuvo un número de 48 pacientes por grupo considerando un 20% de pérdidas. Las características clínicas y demográficas se resumieron con medias, medianas, desviaciones estándar, intervalos, así como frecuencias absolutas y relativas. Para diferencias entre los grupos de tratamiento y control, las variables de tipo dimensional y con distribución normal se analizaron con prueba de t de Student, en aquellas con distribución no-paramétrica se utilizará prueba de U de Mann-Whitney. Para evaluar las diferencias entre variables continuas con distribución no-paramétrica en muestras relacionadas

(antes y después) se utilizó la prueba de rangos de Wilcoxon, en el caso de 3 o más momentos diferentes se utilizó la prueba de Friedman. La incidencia de infecciones bacterianas graves en los diferentes grupos se analizó con curvas de Kaplan-Meier y se compararon con la prueba de log-rank. Las perdidas en el seguimiento se analizaran como fallas. Se realizó análisis por intención de tratar y análisis por protocolo. Se consideró significativo el valor de $p < 0.05$. En el caso de comparaciones múltiples, se realizó corrección de Bonferroni para el valor significativo de *P*, calculado como *P/n*. Todo el análisis estadístico se realizó con el programa estadístico STATA V10 para Mac.

**Resultados**

Un total de 176 pacientes fueron evaluados como posibles candidatos de los cuales 81 pacientes fueron excluidos (figura 1) y los restantes 95 pacientes fueron aleatorizados: 49 (51.6%) en el grupo de ciprofloxacina y 46 (48.4%) en el grupo de tratamiento con placebo. No existieron diferencias en las características basales de los pacientes incluidos en cada grupo las cuales se observan en el cuadro 1. El total de tiempo de seguimiento en los pacientes con ciprofloxacina tuvo una mediana de 18.5 (1-24) semanas. En el grupo de placebo el seguimiento fue de 18 (1-24) semanas (p= NS). En el cuadro 2 se muestran los datos clínicos y de laboratorio al seguimiento.

**Infecciones Bacterianas**

Un total de 16 (32.7%) pacientes en el grupo de ciprofloxacina desarrollaron infecciones bacterianas y 13 (28.3%) en el grupo placebo (p = NS). En el cuadro 3 se

pueden observar los episodios de infecciones en cada grupo. La infección de vías urinarias fue la más frecuente en los pacientes del grupo de ciprofloxacina con significancia estadística en el grupo de mujeres (p = 0.04; cuadros 3 y 4).

Los datos clínicos y de laboratorio al inicio del estudio de los pacientes que desarrollaron una infección en el seguimiento se observan en el cuadro 5. La probabilidad de continuar libre de infecciones no alcanzó diferencias estadísticamente significativa entre los grupos (p= 0.85) (figura 2).

Se documentó un cultivo positivo en 10 pacientes: 7 con IVU (*E. Coli*), 2 en líquido de ascitis (*E. Coli*) y 1 en expectoración (*Staphylococcus aureus).* Todos los pacientes con cultivo positivo, a excepción del paciente con *Staphylococcus aureus*, pertenecen al grupo de ciprofloxacina. Se documentó *E. coli* resistente a ciprofloxacina en 6/7 con IVU, todos ellos fueron tratados con ceftriaxona IV con adecuada respuesta.

**Supervivencia**

La probabilidad de supervivencia a 24 semanas fue menor en el grupo de placebo comparado con los pacientes que recibieron ciprofloxacina sin llegar a tener significancia estadística (p = 0.28; figura 3). Tres pacientes en el grupo de placebo y uno en el grupo de ciprofloxacina murieron durante el periodo de estudio. En todos, la causa de la muerte fue sangrado variceal. Los pacientes en el grupo de placebo murieron a las semanas 10, 18 y 19 de seguimiento. El paciente que murió del grupo de ciprofloxacina ocurrió a la semana 12. La probabilidad de supervivencia a 24 semanas fue de 91% en el grupo placebo y de 98% en el grupo de ciprofloxacina.

## Apego al tratamiento y efectos secundarios

Cuatro pacientes en el grupo de ciprofloxacina y siete pacientes en el grupo de placebo fueron perdidos durante el seguimiento. Cinco pacientes en el grupo de ciprofloxacina tuvieron náusea transitoria pero en ninguno se requirió detener la administración de medicamento. No se documentaron complicaciones directamente relacionadas al uso de ciprofloxacina o placebo. El nivel de significancia en relación con la incidencia de infecciones ($p = 0.83$) y de probabilidad de supervivencia ($P = 0.26$) no se modificó con el análisis por protocolo.

## LPS y citocinas

No existieron diferencias en los niveles séricos entre los pacientes de acuerdo a los diferentes grupos (cuadro 6) de tratamiento. Cuando se agruparon los pacientes de acuerdo al desarrollo de infecciones no se documentaron diferencias en el seguimiento (cuadro 6). Se evidenciaron diferencias en el tiempo en los valores de IL-1 en ambos grupos (ciprofloxacina y placebo; cuadro 7). En el caso de la IL-10, los pacientes que desarrollaron infecciones tuvieron niveles más elevados al seguimiento y se observó una tendencia a la significancia en el caso de IL-6 (tabla 8).

## Discusión

Los resultados del presente estudio no apoyan la eficacia de la profilaxis primaria con ciprofloxacina oral para infecciones bacterianas en pacientes cirróticos con ascitis en ausencia de una indicación actualmente aceptada (niveles de proteínas < 1.5 g/dL en ascitis). El uso de ciprofloxacina en este grupo de pacientes parece reducir la tasa de mortalidad. Los pacientes que recibieron placebo presentaron una mortalidad 3 veces

mayor que los pacientes del grupo de ciprofloxacina. Es posible que en las pacientes mujeres la administración de ciprofloxacina pueda ser deletérea. Finalmente, el uso de ciprofloxacina no mostró un efecto significativo sobre los niveles de LPS o de citocinas séricas.

El uso de antibióticos como profilaxis en pacientes con cirrosis ha sido estudiado previamente y existen criterios para considerar que un paciente en particular es candidato (3, 4, 7-9, 13, 24, 25). En relación con profilaxis primaria, todos los estudios excepto uno (7) fueron diseñados para evaluar la prevención exclusivamente de PBE, sin embargo existe evidencia que prácticamente cualquier infección bacteriana impacta negativamente en la morbilidad y mortalidad de los pacientes con cirrosis (2, 26). Este estudio fue diseñado para evaluar la prevención de cualquier tipo de infección bacteriana. Debido a que los pacientes con cirrosis y ascitis desarrollan deficiencias inmunológicas (18, 19, 27-30) que los predisponen a adquirir infecciones bacterianas con un mayor riesgo de morbi-mortalidad en comparación con la población general (2), evaluamos la eficacia de la ciprofloxacina como profilaxis primaria en pacientes cirróticos sin una indicación actualmente aceptada. De acuerdo a nuestros datos, no existe diferencia en la incidencia de infecciones bacterianas en pacientes que recibieron ciprofloxacina comparados con aquellos que recibieron placebo ($p = 0.64$; cuadro 3). Un resultado interesante es que las mujeres en el grupo de ciprofloxacina tuvieron IVU con mayor frecuencia que las mujeres del grupo de placebo; este resultado no se observó en los hombres (cuadro 4). A pesar de lo anterior, no documentamos una mayor gravedad de los cuadros de IVU en los pacientes del grupo de ciprofloxacina comparado con las pacientes del grupo de

placebo. Como los cuadro de IVU son mas frecuentemente observados en las mujeres, es posible que el uso de ciprofloxacina en este grupo de pacientes pudiera representar un factor de riesgo independiente. La tasa de infecciones en pacientes con cirrosis y profilaxis primaria en estudios previos se reporta entre 13-40% y de 24%-58% en el grupo de placebo (4, 6-8). Nuestros resultados son consistentes con estos datos.

La tasa de mortalidad fue tres veces más alta en los pacientes del grupo placebo comparados con el grupo de ciprofloxacina (figura 3, p = NS) aunque es posible que esta diferencia pudiera ser más evidente con un seguimiento por más tiempo. La mortalidad en este estudio fue menor que lo reportado en algunos estudios previos (4, 6-8). En el estudio de Fernandez *et al* (8) la mortalidad reportada después de tres meses de seguimiento es similar a la cifra reportada en este estudio. En este trabajo la administración de ciprofloxacina fue durante un mes de ahí que es posible que el uso más prolongado de ciprofloxacina pudiera mostrar mejores resultados. Los grupos de tratamiento de los estudios previos recibieron los antibióticos por un tiempo más largo (4, 6-8). Es importante comentar que, en este estudio, 6 de 7 pacientes con cultivo de orina positivo en el grupo de ciprofloxacina tuvieron una *E. Coli* resistente a éste antibiótico; estos pacientes tuvieron un buen desenlace al ser tratados con ceftriaxona. No se observaron diferencias entre los grupos en relación a las complicaciones o apego al tratamiento.

La administración de ciprofloxacina no mostró un efecto considerable sobre el LPS o los niveles de citocinas séricas. Estudios previos has reportado valores séricos de LPS variables y esta falta de consistencia parece estar relacionada con la vida media

corta de esta molécula (31) sugiriendo que el LPS no es un buen marcador de traslocación bacteriana. Por lo anterior, se han investigado otras moléculas como marcadores subrogados de traslocación bacteriana, siendo la proteína fijadora de lipopolisacárido (LBP por sus siglas en ingles; lypopolysacharide-binding protein) la que mejor desempeño ha mostrado (23, 31). La IL-6 es una citocina pro-inflamatoria producida en respuesta a una traslocación bacteriana persistente en los pacientes cirróticos con ascitis (23, 31) y se sabe que esta involucrada en el daño celular, muerte de hepatocitos, colestasis y fibrosis hepática (29, 30). En relación a la IL-10 al ser una citocina anti-inflamatoria, se podría esperar una secreción elevada como mecanismo de compensación en aquellos pacientes con desarrollo de infección y como respuesta a la traslocación bacteriana persistente. La variabilidad en los niveles séricos de citocinas pudiera estar relacionada con factores asociados a las características de los pacientes incluidos en estudios previos. En el estudio de Albillos *et al* se incluyeron controles sanos, pacientes cirróticos con ascitis y pacientes cirróticos sin ascitis. Los niveles séricos de TNF e IL-6 en los pacientes incluidos en este estudio son similares a los reportados por Albillos *et al* en el grupo de pacientes cirróticos con ascitis y niveles elevados de LBP. En el estudio de Berry *et al* se reportaron niveles más elevados de TNF, IL-6 e IL-10 que los reportados por Albillos *et al* y a los encontrados en el presente estudio, estas diferencias pudieran explicarse debido a que Berry *et al* incluyeron pacientes con cirrosis descompensada y complicaciones agudas al momento de la inclusión (30).

Debido a la traslocación bacteriana, la descontaminación intestinal con antibióticos pudieras tener un impacto en los niveles séricos de las citocinas pro-inflamatorias.

Sin embargo, nuestros resultados no apoyan esta hipótesis en pacientes con ascitis “compensada”. Esto pudiera estar en relación con la vida media de las citocinas en el torrente sanguíneo, la presencia de diferentes estímulos para la producción de citocinas así como a una vigorosa, pero permanente, respuesta de exposiciones previas a LPS. En relación con los niveles séricos de IL-1, los valores obtenidos fueron inestables en ambos grupos. La explicación a éste fenómeno parece ser una inestabilidad propia de la citocina más que al uso de la ciprofloxacina. En el caso de la IL-6 y de la IL-10 se observaron diferencias entre los valores antes-después en los pacientes que desarrollaron infecciones (cuadro 8). Estas diferencias no se observaron en relación al uso de ciprofloxacina (cuadro 7). Cuando los pacientes con infecciones más graves (PBE y neumonía) fueron analizados como grupo y comparados con los pacientes con otras infecciones, no se evidenciaron diferencias en los niveles de LPS o citocinas.

Algunas limitaciones de nuestro estudio se deben considerar: 1) se incluyeron pacientes con diferentes etiologías de cirrosis, 2) no se incluyeron pacientes con niveles altos de Child-Pugh (específicamente pacientes con 14 y 15 puntos), y 3) el tiempo de administración de ciprofloxacina fue relativamente corto. Al incluir pacientes con diferentes etiologías de cirrosis es posible que erróneamente se estudien pacientes con diferentes grados de compromiso inmunológico. Aunque algunos pacientes (por ejemplo aquellos con VHC) tienen manifestaciones extra-hepáticas mediadas por fenómenos inmunológicos, hasta nuestro conocimiento, no existen datos que apoyen la idea de que un grupo en particular de cirróticos es más susceptible a infecciones en comparación a pacientes con cirrosis de otras etiologías.

Los pacientes con cirrosis con alteraciones inmunológicas bien conocidas debido a la etiología de la hepatopatía (hepatitis autoinmune, cirrosis biliar primaria, síndrome de sobreposición) o por tratamientos recibidos (inmunosupresores) no fueron incluidos en éste estudio. Se decidió excluir pacientes con una indicación de profilaxis primaria aceptada actualmente debido a que consideramos que existe suficiente evidencia para ello y pensamos que era más relevante estudiar grupos diferentes en los cuales el efecto de ciprofloxacina (u otros antibióticos) pudiera ser relevante pero desconocido hasta éste momento. Debido a la incertidumbre propia de ser el primer estudio en este grupo de pacientes con el uso de profilaxis primaria y aunque estudios previos han utilizado antibióticos por periodos más largos de manera segura (3, 4, 6-8, 25), decidimos utilizar la ciprofloxacina por un tiempo que pudiera minimizar la probabilidad de efectos secundarios, específicamente las infecciones causadas por bacterias resistentes o por hongos. Es posible que estudios futuros con diferentes esquemas de profilaxis muestren resultados favorables en el desarrollo de infecciones y en la mortalidad en éste grupo de pacientes. Nuestros resultados son consistentes con resultados previos (27) en relación a la idea de que los pacientes con cirrosis se encuentran en un estado basal de hiperestimulación para la producción de citocinas y que hasta cierto punto carecen de reservas que les permitan una mayor respuesta ante estímulos nuevos (27).

En conclusión, la profilaxis primaria con ciprofloxacina en pacientes con cirrosis y ascitis que no tienen una indicación actualmente aceptada no muestra un efecto preventivo en el desarrollo de infecciones bacterianas. La ciprofloxacina como

profilaxis primaria parece disminuir la mortalidad en pacientes cirróticos pero incrementa el riesgo de Infecciones de vías urinarias en el grupo de mujeres.

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Cuadro 1. Características clínicas y de laboratorio basales de los pacientes clasificados por grupos de tratamiento.

| Característica | Ciprofloxacina n = 49 | Placebo n = 46 | *Valor de P* |
|---|---|---|---|
| Hombre:Mujer | 15:34 | 22:24 | 0.062 |
| Etiología de la cirrosis | | | |
| HCV | 30 (60) | 28 (61) | |
| Alcohol | 7 (15) | 10 (22) | 0.543 |
| Criptogénica | 11 (23) | 6 (13) | |
| HBV | 1 (2) | 2 (4) | |
| Child-Pugh-Turcotte | | | |
| A | 7 (14) | 7 (15) | |
| B | 31 (63) | 31 (67) | 0.756 |
| C | 11 (23) | 8 (17) | |
| Diabetes mellitus | 9 (27) | 11 (29) | 0.876 |
| Edad, *años* | 56.7 ± 13.2 | 56.3 ± 11.7 | 0.814 |
| IMC, $kg/m^2$ | 26.2 ± 4.1 | 26.6 ± 4.3 | 0.671 |

| | | | |
|---|---|---|---|
| Seguimiento, *semanas* | 24.9 (1-48.9) | 22.4 (1.9-40) | 0.477 |
| Child-Pugh-Turcotte, puntaje | 8.1 ± 1.6 | 8.0 ± 1.8 | 0.607 |
| MELD, puntaje | 12.9 ± 3.8 | 12.4 ± 2.5 | 0.417 |
| Albúmina, g/dL | 2.8 ± 0.6 | 2.9 ± 0.6 | 0.249 |
| Bilirrubina total, mg/dl | 2.2 ±1.3 | 2.08±1.2 | 0.54 |
| Leucocitos, $mm^3$ | 4 ± 1.9 | 4.3 ± 1.7 | 0.531 |
| Neutrófilos, $mm^3$ | 2.5 ± 1.4 | 2.7 ± 1.4 | 0.419 |
| Linfocitos, $mm^3$ | 1.0 ± 0.6 | 1.0 ± 0.6 | 0.875 |
| Monocitos, $mm^3$ | 0.4 ± 0.5 | 0.4 ± 0.34 | 0.804 |
| Hemoglobina, g/dL | 12.5 ± 2.2 | 12.4 ± 2.3 | 0.692 |
| Plaquetas, $mm^3$ | 88 ± 45 | 86 ± 47.7 | 0.867 |
| Creatinina, mg/dL | 0.86 ± 0.3 | 0.98 ± 0.67 | 0.284 |

Las características basales están expresadas como n (%) y las variables contínuas como ($\bar{x} \pm s$) o medianas (intervalos mínimo-máximo). HCV: virus de hepatitis C, HBV: virus de hepatitis B, IMC: índice de masa corporal, MELD: Model for End-stage Liver Disease

Cuadro 2. Características clínicas y de laboratorio al seguimiento de los pacientes clasificados por grupos de tratamiento

| Característica | Ciprofloxacina n = 49 | | | Placebo n = 46 | | |
|---|---|---|---|---|---|---|
| | Sem 4 | Desenlace | *Valor de P* | Sem 4 | Desenlace | *Valor de P* |
| Child-Pugh-Turcotte | 8±1.6 | 8.2±1.8 | 0.35 | 7.5±1.6 | 7.9±1.9 | 0.04 |
| Albumina, g/dL | 2.3±0.7 | 2.7±0.54 | 0.42 | 2.1±0.7 | 2.9±0.57 | 0.75 |
| Leucocitos, $mm^3$ | 4.2±3.1 | 3.9±2 | 0.41 | 3.6±1.5 | 5.3±4.4 | 0.29 |
| Neutrófilos, $mm^3$ | 2.8±2.9 | 2.8±1.9 | 0.45 | 2.4±0.98 | 3.4±4 | 0.27 |
| Linfocitos, $mm^3$ | 0.12±0.09 | 0.11±0.06 | 0.41 | 0.11±0.04 | 0.15±0.13 | 0.29 |
| Monocitos, $mm^3$ | 0.34±0.18 | 0.26±0.14 | 0.42 | 0.30±0.16 | 0.38±0.26 | 0.10 |
| Hemoglobina, g/dL | 12.4±2.2 | 11.7±2.4 | 0.11 | 12.6±6.6 | 12.2±2.6 | 0.6 |
| Plaquetas, $mm^3$ | 75.9±38.5 | 76±31 | 0.14 | 72.8±33 | 89±43 | 0.08 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Creatinina, mg/dL | 0.89±0.4 | 0.97±0.5 | 0.30 | 0.87±0.37 | 0.92±0.3 | 0.78 |

Las características basales están expresadas como n (%) y las variables contínuas como ($\bar{x} \pm s$) o medianas (intervalos mínimo-máximo). Sem = semanas.

Cuadro 3. Incidencia y tipo de infecciones en cada grupo, n (%)

| Infección | Ciprofloxacina n = 49 | Placebo n = 46 | *Valor de P* |
|---|---|---|---|
| Urinaria | 7 (14) | 0 | |
| Respiratoria | 2 (4) | 6 (13) | |
| Gastrointestinal | 4 (8) | 4 (9) | |
| Sinusitis | 0 | 2 (4) | 0.025 |
| Peritonitis bacteriana espontánea | 2 (4) | 0 | |
| Absceso Dental | 1 (2) | 1 (2) | |
| TOTAL | 16 (32.7) | 13 (28.3) | 0.64 |

Cuadro 4. Riesgo de infección de vías urinarias de acuerdo al sexo y grupo de tratamiento

| | Ciprofloxacina n = 16 | Placebo n = 13 | RR (IC95%) | *Valor de P* |
|---|---|---|---|---|
| Mujeres | | | | |
| IVU | 6 | 0 | 2.17 | 0.046 |
| No-IVU | 7 | 8 | (1.25-3.67) | |
| Hombres | | | | |
| IVU | 1 | 0 | 3.49 | 0.37 |
| No-IVU | 2 | 5 | (0.98-11) | |

IVU: infección de vías urinarias, RR = riesgo relativo, IC95%≡ intervalo de confianza al 95%.

Cuadro 5. Características clínicas y bioquímicas basales de los pacientes que desarrollaron infecciones de acuerdo al tratamiento recibido

| Característica | Ciprofloxacina n = 16 | Placebo n = 13 | *Valor de P* |
|---|---|---|---|
| Hombre:Mujer | 3:13 | 5:8 | 0.40 |
| Etiología de la cirrhosis | | | |
| HCV | 11 (69) | 9 (69) | |
| Alcohol | 2 (13) | 1 (8) | |
| Criptogénica | 2 (13) | 2 (15) | 0.97 |
| HBV | 1 (6) | 1 (8) | |
| Child-Pugh-Turcotte | | | |
| A | 2(12.5) | 0 | |
| B | 12 (75) | 11 (85) | 0.41 |
| C | 2(12.5) | 2 (15) | |
| Diabetes mellitus | 4 (25) | 3 (23) | 0.88 |
| Edad, *años* | 56.1 ±13.4 | 56.1 ±12.7 | 0.99 |
| IMC, $kg/m^2$ | 25.9 ± 4.4 | 25.8 ± 3.4 | 0.96 |

| | | | |
|---|---|---|---|
| Seguimiento, *semanas* | 15.3 ± 7.2 | 11 ± 6.4 | 0.10 |
| Child-Pugh-Turcotte, *puntaje* | 7.9 ± 1.2 | 8.1 ± 1.2 | 0.56 |
| MELD, *puntaje* | 11.9 ± 2.1 | 13 ± 2 | 0.48 |
| Albúmina, g/dL | 2.6 ± 0.5 | 2.8 ± 0.5 | 0.35 |
| Bilirrubina total, mg/dl | 1.9±1 | 1.9±1 | 0.95 |
| Leucocitos, $mm^3$ | 3.7 ± 1.2 | 4.4 ± 1.7 | 0.24 |
| Neutrófilos, $mm^3$ | 2.3 ± 0.6 | 2.7 ± 1.1 | 0.18 |
| Linfocitos, $mm^3$ | 0.9 ± 0.67 | 1 ± 0.4 | 0.69 |
| Monocitos, $mm^3$ | 0.33 ±0.17 | 0.40 ±0.25 | 0.34 |
| Hemoglobina, g/dL | 12.7 ± 2.1 | 12.3 ± 1.8 | 0.66 |
| Plaquetas, $mm^3$ | 86.6 ± 46 | 80.4 ± 36 | 0.69 |
| Creatinina, mg/dL | 0.93 ± 0.4 | 1 ± 0.3 | 0.47 |

Las características basales están expresadas como n (%) y las variables contínuas como ($\bar{x} \pm s$) o medianas (intervalos mínimo-máximo). HCV: virus de hepatitis C, HBV: virus de hepatitis B, IMC: índice de masa corporal, MELD: Model for End-stage Liver Disease

Cuadro 6. Niveles séricos basales de LPS y citocinas clasificando a los pacientes por grupo de tratamiento y desarrollo de infecciones.

| Citocina | Ciprofloxacina n = 49 | Placebo n = 46 | *P* value | Infección +vo n = 29 | Infección –va n = 66 | *Valor de P* |
|---|---|---|---|---|---|---|
| LPS, EU/mL | 16.5 (0-55) | 24.4 (0-160) | 0.05 | 16 (0.2-56) | 14.3 (0.1-160) | 1 |
| TNF$\alpha$,pg/mL | 8(8-37) | 8(8-118) | 0.91 | 8(8-19) | 8(8-118) | 0.37 |
| IL-1, pg/mL | 4(4-43) | 4(4-110) | 0.4 | 4(4-39) | 4(4-110) | 0.86 |
| IL-6, pg/mL | 30(4-428) | **30(4-247)** | 0.17 | 28(4-135) | 31(4-428) | 0.7 |
| IL-10, pg/mL | 8.6(4-102) | 9(4-143) | 0.96 | 8(4-126) | 10(4-143) | 0.70 |
| IL-12, pg/mL | 225 (30-2573) | **258 (30-3890)** | 0.88 | 296 (30-2573) | 202 (27-3890) | 0.23 |

Los valores están expresados como medianas (intervalo mínimo-máximo). LPS: lipopolisacárido, TNFa = factor de necrosis tumoral alfa, IL-1 = interleucina 1, IL-6 = interleucina 6, IL-10 = interleucina 10, IL-12 = interleucina 12.

Cuadro 7. Diferencias en los niveles séricos de LPS y citocinas a la semana 4 y al desenlace comparados con los niveles basales clasificando a los pacientes de acuerdo a la maniobra recibida (expresados como porcentaje de cambio)

| | Ciprofloxacina n = 49 | | | Placebo n = 46 | | |
|---|---|---|---|---|---|---|
| Citocina | Basal-sem 4 | Basal-desenlace | *Valor P* | Basal-sem 4 | Basal-desenlace | *Valor P* |
| LPS, pg/mL | 6 (-29-24) | -2 (-75-30) | 0.24 | -25(-59-14) | -19 (-100-15) | 0.71 |
| TNFα, pg/mL | 0 (0-0) | 0 (0-0) | 0.63 | 0 (-0-0) | -0 (0-0) | 0.68 |
| IL1, pg/mL | 0 (-64-0) | 0 (-59-0) | 0.001 | 0 (-37-0) | 0 (-7-0) | 0.05 |
| IL6, pg/mL | 0.7 (-29-45) | 54 (-34-132) | 0.062 | 5 (-20-50) | -.7 (-24-106) | 0.90 |
| IL10, pg/mL | 3 (-1-46) | 0 (-8.8-38) | 0.20 | 0 (-22-38) | 0 (-11-59) | 0.47 |
| IL12, pg/mL | **-.37 (-17-21)** | 3 (-17-31) | 0.66 | -1 (-18-21) | 0 (-28-43) | 0.93 |

Los valores están expresados como medianas (percentil25-percentil75). Sem = semana, LPS: lipopolisacárido, TNFa = factor de necrosis tumoral alfa, IL-1 = interleucina 1, IL-6 = interleucina 6, IL-10 = interleucina 10, IL-12 = interleucina 12.

Cuadro 8. Diferencias entre los niveles séricos de LPS y citocinas a la semana 4 y al desenlace comparados con el basal clasificando a los pacientes de acuerdo al desarrollo de infecciones (expresados en porcentaje de cambio)

| | Pacientes con infección n = 29 | | | Pacientes sin infección n = 66 | | |
|---|---|---|---|---|---|---|
| Citocina | Basal-sem 4 | Basal-desenlace | *Valor P* | Basal-sem 4 | Basal-desenlace | *Valor P* |
| LPS, pg/mL | 5 (-100-3000) | 0,7 (-100-765) | 0.62 | -11 (-100-905) | -10 (-100-304) | 0.10 |
| TNFα, pg/mL | 0 (0-0) | 0 (0-0) | 0.89 | 0 (-3-0) | 0 (0-0) | 0.27 |
| IL1, pg/mL | 0 (-79-0) | 0 (-28-0) | 0.50 | 0 (-42-0) | 0 (-41-0) | 0.22 |
| IL6, pg/mL | 0 (-24-65) | 68 (-30-601) | 0.073 | 2 (-25-44) | -0.4 (-30-135) | 0.10 |
| IL10, pg/mL | 0 (-20-55) | 18 (-6-306) | 0.012 | 0 (-8-43) | 0 (-10-31) | 0.39 |
| IL12, pg/mL | -4(-20-26) | -6 (-24-15) | 0.33 | 0 (-12-21) | 5 (-23-47) | 0.92 |

Los valores están expresados como medianas (percentil25-percentil75). Sem = semana, LPS: lipopolisacárido, TNFa = factor de necrosis tumoral alfa, IL-1 = interleucina 1, IL-6 = interleucina 6, IL-10 = interleucina 10, IL-12 = interleucina 12.

176 Posibles Candidatos

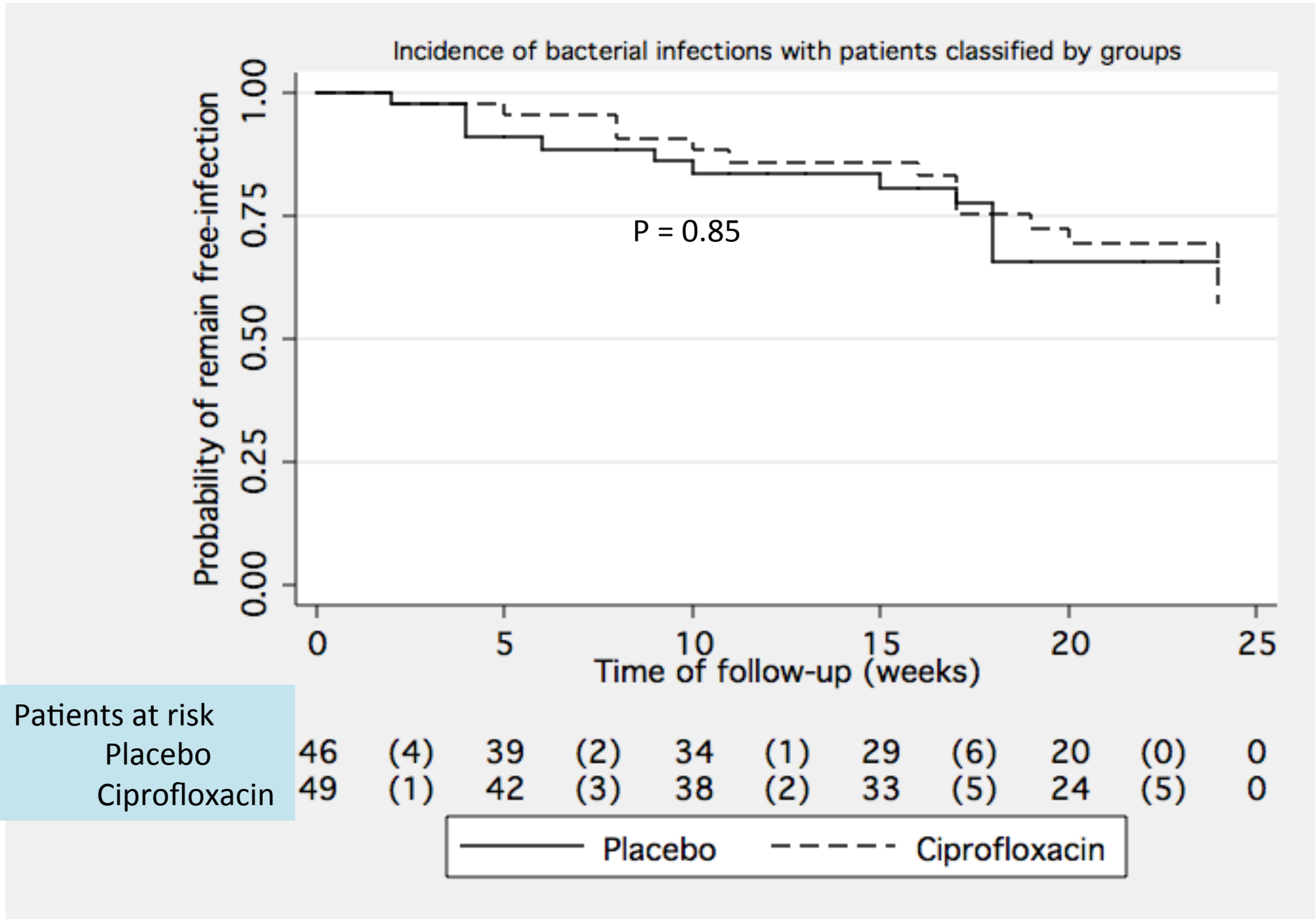
Pacientes excluidos 81

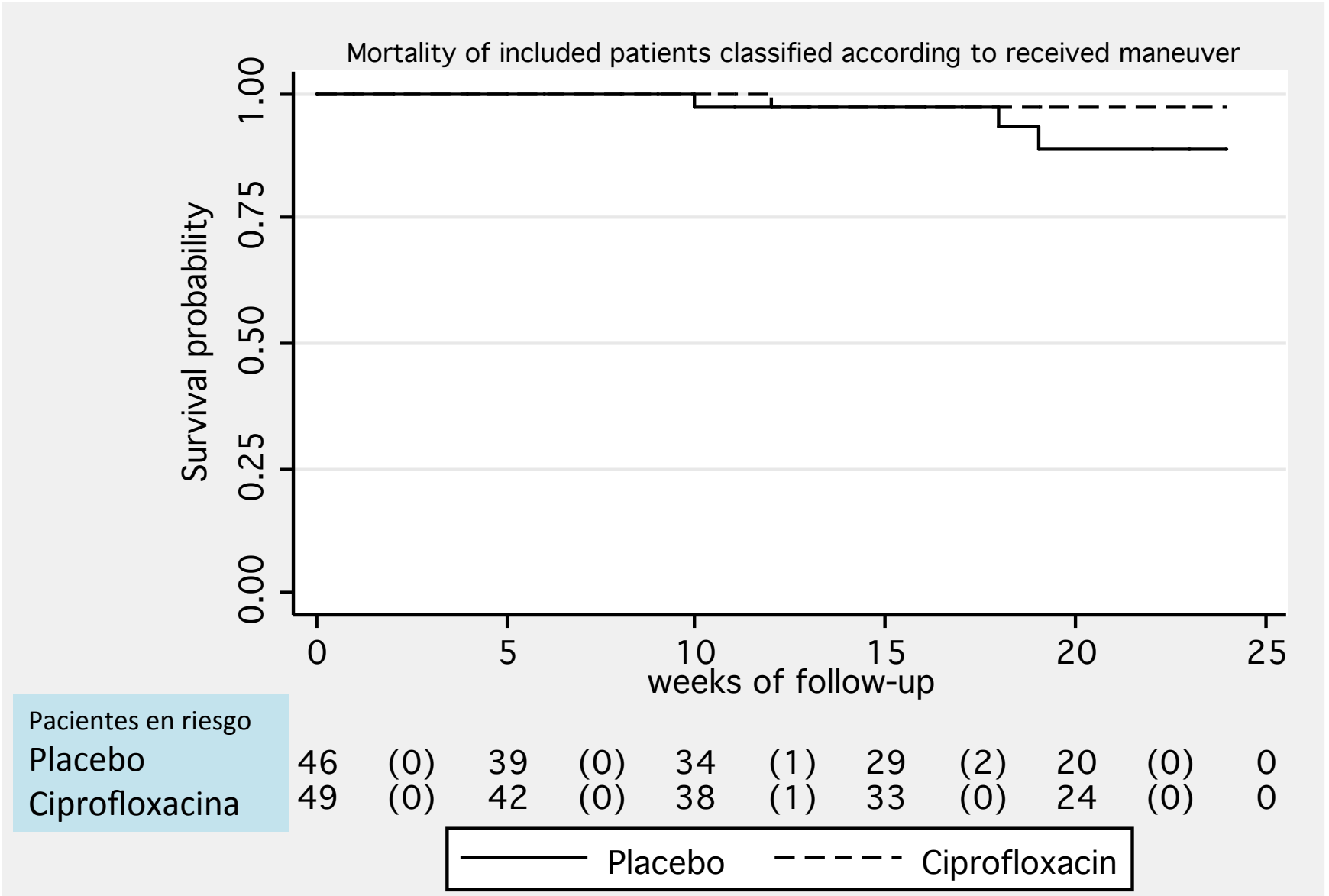
- No posibilidad de seguimiento 25
- Uso de antibióticos 12
- No aceptaron participar 10
- Child-pugh alto 10
- Infección activa8
- Alergia 7
- Enfermedad autoinmune 5
- Consumo actual de alcohol 2
- Probable CHC2

**95 Pacientes aleatorizados**

**ciprofloxacina 49**

**Placebo 46**


Incidence of bacterial infections with patients classified by groups
Probability of remain free-infection
0.00
0.25
0.50
0.75
1.00
P = 0.85
0
5
10
15
20
25
Time of follow-up (weeks)
Patients at risk
Placebo 46 (4) 39 (2) 34 (1) 29 (6) 20 (0) 0
Ciprofloxacin 49 (1) 42 (3) 38 (2) 33 (5) 24 (5) 0
Placebo
Ciprofloxacin


Mortality of included patients classified according to received maneuver
Survival probability
0.00
0.25
0.50
0.75
1.00
0
5
10
15
20
25
weeks of follow-up
Pacientes en riesgo
Placebo 46 (0) 39 (0) 34 (1) 29 (2) 20 (0) 0
Ciprofloxacina 49 (0) 42 (0) 38 (1) 33 (0) 24 (0) 0
Placebo
Ciprofloxacin

# ANEXOS

# Artículos en Extenso

ANNALS of Hepatology

ORIGINAL ARTICLE

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# Rapid diagnosis of spontaneous bacterial peritonitis using leukocyte esterase reagent strips in Emergency Department: Uri-Quick Clini-10SG® *vs.* Multistix 10SG®

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**ABSTRACT**

**Background and aim.** Bacterial peritonitis (SBP) is the most frequent infection in patients with cirrhosis causing significant mortality. Delay in SBP diagnosis is a serious problem. The aim of this study was to evaluate the diagnostic yield of Uri-Quick Clini-10SG® *vs.* Multistix 10SG® reagent strips in an Emergency Department. **Material and methods.** A prospective study of consecutive patients with ascites and paracentesis attending to Emergency Department from March 2005 to February 2007 was made. SBP was defined by ≥ 250 neutrophiles /mm$^3$. The ascites obtained at bedside was immediately tested in a dry test tube with both the Uri-Quick Clini 10SG® and MultistixSG10®. The Uri-Quick Clini 10SG® and Multistix SG10®. Strips were considered positive at grade ≥ 3 (≥125 leukocytes/mL). **Results.** A total of 223 ascitic fluid samples were obtained. There were 49 episodes of SBP. Median age was 54 (range 18-87 year) years; 62.3% were female. The sensitivity, specificity, PPV, NPV, and 95% CI for Uri-Quick Clini 10SG® were 79.6 (64-87), 98.2 (94-99), 90.5 (78-96) and 93.9 (89-96), respectively. For MultistixSG10® the values were 77.5 (64-88), 97.7 (93-98), 90 (77.9-96.2), and 94 (89.4-96.6), respectively. **Conclusion.** The use of reagent strip is useful for SBP diagnosis in an emergency setting. The high PPV allow start antibiotic treatment. In areas without the resources to perform conventional ascites fluid analyses, these strips could be presently used.

**Key words.** Infection. Diagnosis. Ascites. Liver cirrhosis.

## INTRODUCTION

Infections in cirrhotic patients are the major cause of hospitalization and death, being responsible until 30 and 50% of cases, respectively.[1] Spontaneous bacterial peritonitis (SBP) is the most frequent infection in these patients.[2] The gold standard for the diagnosis of SBP is the neutrophile count in ascites fluid, defined by polymorphonuclear (PMN) count of ≥ 250 cell/mm$^3$.[3] Unfortunately the manual cellular count with special smears, actual method for SBP diagnosis is a laborious and time-dependent procedure, and expertise is required.[4] If this resource is not available, a delay in diagnosis and treatment exposes patients to a high risk of death, whereas the systematic use of empirical large spectrum antibiotics leads to unjustified iatrogenic or nosocomial complications, and increased medical cost.

The leukocyte esterase reagent strips are special devices that allow leukocyte detection in different biological fluids via a colorimetric reaction.[5,6] There are previous reports that describe the use of test strips to make an "instant" diagnosis of SBP.[7,8] However, the reagent strips used in these previous reports are scarce and difficult to obtain in our environment. Therefore, we assessed their diagnostic accuracy of two different reagent strip in an emergency setting with a big sample, using multiple observers.

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## MATERIAL AND METHODS

### Patients

All consecutive patients attending Emergency Department with ascites and paracentesis from March 2005 to February 2007 were included. Asymptomatic patients and patients with SBP suspicion were included. SBP was defined by PMN count of ≥ 250 cell/mm$^3$. Paracentesis were performed on admission as dictated by standard medical practice, and repeated as indicated. These included diagnostic paracentesis alone, or combined therapeutic and diagnostic. The ascites obtained at bedside was immediately tested in a dry test tube with both the Uri-Quick Clini 10SG® (Stanbio Laboratory, Texas, USA) and MultistixSG10® (Bayer diagnostics, Bridgend, UK) strips, according to the manufacturer's guidelines for urine testing: strips were immersed in the ascitic fluid, immediately removed and after the required waiting period the color of the reagent square corresponding to leukocytes was compared with the color chart on the bottle. The Uri-Quick Clini 10SG® is read at 120 s and is either negative or four-tier positive (+1 to +3). The MultistixSG10s is read at 120 s and is either negative or four-tier positive (trace, +1 to +3). The strips were considered positive at grade 3 (125 leukocytes/mL), because grade 4 is above the cutoff defining SBP. Two physicians participated in reading the strips, one of them in patient's charge. In all cases both physician were unaware of the results of ascites manual cellular count. All ascites fluid samples were then processed in the hospital laboratory for manual cell count with differential, ascitic fluid culture and biochemistry. Cultures were performed using 10 mL of fluid in aerobic and anaerobic media blood culture bottles. Antibiotic therapy was initiated if the ascites fluid PMN cell count was ≥ 250/mL.

### Statistical analysis

Results of leukocyte esterase reagent strip testing were compared with leukocyte (total count) and PMN counts, ascitic fluid culture and biochemical analysis and clinical data in all patients. Sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV) and likelihood ratios of each reagent strip in the diagnosis of SBP were calculated. 95% confidence intervals for proportions were calculated. Likelihood ratios were weighted by prevalence. Concordance between investigator and physician on patient's charge readings and between reagent strips was also evaluated using the kappa statistic (κ). All analyses were conducted using the statistics program SPSS/PC version 12.0 (Chicago, IL, USA).

## RESULTS

Two-hundred and twenty-nine ascites fluid samples were obtained of 138 patients during 48 months. Six samples were excluded because does not have manual cellular count. There were 49 episodes of SBP. The median number of samples/patient was 1 (range 1-7). Median age was 54 (range 18-87) years; 62.3% were female; and 4 (2.9%) were Child A, 51 (37%) were Child B and 83 (60.1%) were Child C. Cirrhosis was caused by chronic hepatitis C in 29.7% of cases, autoimmune hepatitis on 13%, cryptogenetic cirrhosis on 11.6%, alcohol in 7%, 19.6% of patients were cirrhosis under diagnosis process and others causes in 19%. At the time of fluid collection 59 cases (26.5%) were associated with a presumptive diagnosis of SBP.

Total cell count ranged from 0 to 11,800/mm$^3$. Forty-nine samples (21.9%) had an ascites PMN count ≥ 250/mL (range: 255-10,620), obtained in 40 patients with total counts ranging from 267 to 11,800. Of these 49 cases, 14 (28.5%) were associated with positive ascites cultures. Of the 49 patients with SBP, 39 (79.6%) had had the presumptive diagnosis of SBP. Four patients diagnosed with SBP were under prophylaxis at the time of diagnosis.

In all 223 samples, when results were expressed as either positive or negative, the readings of the two physicians concurred 100%. Table 1 shows the sensitivity, specificity, PPV, NPV, likelihood ratio for a positive test, likelihood ratio for a negative test, and 95% CI when we considered a reagent strip positive with grade 3. When results were characterized,

**Table 1.** Sensitivity, specificity, PPV, NPV, LRPT, LRNT, and 95% CI when we considered a reagent strip positive with grade 3.

| Parameter | Uri-Quick Clini 10SG® | MultistixSG10® |
|---|---|---|
| Sensitivity | 79.6 (64-87) | 77.5 (64-88) |
| Specificity | 98.2 (94-99) | 97.7 (93-98) |
| PPV | 90.5 (78-96) | 90 (77.9-96.2) |
| NPV | 93.9 (89-96) | 94 (89.4-96.6) |
| LRPT | 33.7 (13-90) | 33.6 (12.66-89.91) |
| LRNT | 0.22 (.13-.38) | 0.23 (0.14-0.39) |

PPV: positive predictive value. NPV: negative predictive value. LRPT: likelihood ratio for a positive test. LRNT: likelihood ratio for a negative test.

**Table 2.** Discordant results obtained from ascitic samples with leukocyte esterase reagent strip according manual cellular count result as gold standard.

| Patient number | False negatives Total cell count | Total PMN | Patient number | False positives Total cell count | Total PMN |
|---|---|---|---|---|---|
| 55* | 1,500 | 1,350 | 72§ | 0 | - |
| 58 | 590 | 266 | 86 | 47 | - |
| 64 | 375 | 311 | 90† | 247 | 245 |
| 76 | 1,800 | 1,530 | 116† | 255 | 150 |
| 92 | 625 | 363 | 197 | 545 | 114 |
| 100 | 452 | 447 | - | - | - |
| 111 | 497 | 472 | - | - | - |
| 114 | 497 | 462 | - | - | - |
| 122 | 407 | 366 | - | - | - |
| 150 | 267 | 256 | - | - | - |
| 187 | 507 | 456 | - | - | - |

*Negative only with Multistix 10SG® strip. †Positive only with Multistix 10SG® strip. § Positive only with Uri-Quick Clini-10SG® strip.

as either positive or negative, kappa value was 0.94; $p < 0.001$.

For patients without *a priori* clinical or biological signs of infection (164 patients; 73.5%), sensitivity was 77.2%, specificity was 98.5%, PPV 89.4%, and NPV 96.5% for Uri-Quick Clini 10SG®. For MultistixSG10® strips sensitivity was 77.2%, specificity was 97.8%, PPV 85%, and NPV 96.5%.

In table 2 are shown discordant results (negative and positive false) obtained from ascitic samples with leukocyte esterase reagent strip according manual cellular count result as gold standard.

## DISCUSSION

This study represents the first report from a Latin American center of diagnostic yield of a reagent strip easily available in our environment and the only one in worldwide, for our knowledge, with patients exclusively arising from an emergency department. According with our results the Uri-Quick Clini 10SG® and MultistixSG10® strips are both useful for a rapid SBP diagnosis in an emergency setting. These data are according with previous reports.[7,8]

The rapidity in diagnosis is an important issue in SBP because it could, as similar as with other septic patients, it represents an early treatment application with a potential positive effect morbi-mortality.[1] Delay in diagnosis because the scarcity of trained personal, and therefore treatment of patients with SBP is an important problem previously reported.[4] According with our results, use of reagent strips available in our environment could be use to decide about to initiate treatment or continue the diagnostic approach of cirrhotic patients attending Emergency Department. The positive predictive value of reagent strips allow start treatment without considerable risk to unjustified iatrogenic, nosocomial complications, or increased medical cost. The negative predictive value, however, for be a high mortality-disease is not enough for discard SBP. In terms of the severity of SBP, the rate of false-negative results could be considered high.

The test with Uri-Quick Clini 10SG® may help the clinician in some circumstances when a cell count is not available within a few hours. These reagent strips may be useful in developing countries without sufficient resources. The cost of the strip is only 0.50USD.

We chose to use in this study the Uri-Quick Clini 10SG® for several reasons: there is no previous study with this strip and this test is widely available in public institutions in Mexico. Nonetheless, other reagent strips can be used with greater accuracy. Castellote, *et al.*[9] used Aution sticks® manufactured in Italy and observed 89% sensitivity. However, these strips are not available in our country. To our knowledge, no study had yet compared Aution sticks® and Uri-Quick Clini 10SG® strips. Sapey, *et al.*,[10] compared the Multistix 10 SG® and the Nephur test® and showed that the Nephur test® was more sensitive (88.2 *vs.* 64.7%). The Combur test®, which is a modified version of the Nephur test®, has also been recently compared with the Multistix® in 2 studies.[8,11] The sensitivity of the tests was identical in the study by Thevenot, *et al.*,[8] whereas the Combur® test was more sensitive than the Multistix® test in the first when using the threshold of grade 2 on a colorimetric scale (63.0 *vs.* 45.7%).[11]

These results support the need to evaluate the strips easy-available in our environment. In a previous review article that summarize published related articles the authors concludes that the use of reagent strips for the diagnosis of SBP cannot be recommended because low sensitivity, especially in patient with low PMN count, however is important to consider that any of the included studies in that review was carried-out using Uri-Quick Clini 10SG® strips.[12] More recent papers (one systematic review, and editorial and one with original data) conclude that there is reasonable amount of evidence to support the use of reagent strips in the work-up of patients suspected of having SBP mainly in poorer were ascitic fluid testing may not be readily available.[13-15]

One limitation of our study is the subjectivity of the reading strip, common to all colorimetric tests.

In summary, the use of reagent strip is useful for SBP diagnosis in an emergency setting. The high PPV allow start treatment without concern about possible collateral effects, however because the severity of disease and the NPV of the test we do not recommend ruleout SBP diagnosis in a patient with negative reagent strip test but a clinical presentation suggestive of SBP. We do not suggest that standard ascites fluid analyses be systematically replaced by the use of leukocyte esterase reagent strips. Nonetheless, in areas without the resources to perform ascites fluid analyses, these strips could be presently used.

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En este trabajo se concluye que el uso de tiras reactivas para detectar leucocitos en orina pueden ser de utilidad para el diagnóstico de peritonitis bacteriana espontánea en los departamentos de Urgencias.

El estudio se desarrolló como respuesta a la realidad de que no todos los hospitales que atienden pacientes con cirrosis hepática cuentan, en todos los horarios y días de la semana, con personal capacitado para llevar a cabo la cuenta celular en ascitis. Ello conlleva a retrasos en el diagnóstico y tratamiento de una patología con alta mortalidad. Con nuestro estudio justificamos el uso de las tiras como un método barato, disponible y rápido para diagnosticar la enfermedad e iniciar el tratamiento en cuestión de minutos.

**Citas recibidas a este trabajo: cero**

AP&T Alimentary Pharmacology and Therapeutics

# Meta-analysis: antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding – an updated Cochrane review

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## SUMMARY

### Background
Antibiotic prophylaxis seems to decrease the incidence of bacterial infections in patients with cirrhosis and upper gastrointestinal bleeding and is considered standard of care. However, there is no updated information regarding the effects of this intervention.

### Aim
To assess the benefits and harms of antibiotic prophylaxis in cirrhotic patients with gastrointestinal bleeding by performing a systematic review of randomised trials.

### Methods
We searched The Cochrane Hepato-Biliary Group Controlled Trials Register, The Cochrane Central Register of Controlled Trials in The Cochrane Library, MEDLINE, EMBASE and Science Citation Index EXPANDED until June 2010. We statistically combined data calculating relative risk (RR) for dichotomous outcomes and mean difference (MD) for continuous outcomes.

### Results
Twelve trials (1241 patients) evaluating antibiotic prophylaxis against placebo or no antibiotic prophylaxis were included. Antibiotic prophylaxis was associated with reduced mortality (RR 0.79, 95% CI 0.63–0.98), mortality from bacterial infections (RR 0.43, 95% CI 0.19–0.97), bacterial infections (RR 0.35, 95% CI 0.26–0.47), rebleeding (RR 0.53, 95% CI 0.38–0.74) and days of hospitalisation (MD −1.91, 95% CI −3.80–0.02). Trials analysing rebleeding rate and hospitalisation length are still scarce, thus, caution should be exerted when interpreting the results.

### Conclusions
Antibiotic prophylaxis in patients with cirrhosis and upper gastrointestinal bleeding significantly reduced bacterial infections, and reduce all-cause mortality, bacterial infection mortality, rebleeding events and hospitalisation length. Novel clinically significant outcomes were included in this meta-analysis. Some benefits are biased and the risks are not yet properly assessed, this encourages future research in this field.

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## INTRODUCTION

Around one-third of cirrhotic patients will experience bleeding from oesophageal or gastro-oesophageal varices, with 70% recurrence rate and 20% fatality rate.[1] The highest mortality peak is observed during the first 6 weeks after the bleeding episode, being mainly associated with hepatic functional status, renal dysfunction and bacterial infections.[2, 3] Consequently, guidelines for treatment of patients suffering variceal gastrointestinal bleeding include volume expansion, haemorrhage control, use of vasoconstrictors and short-term antibiotic prophylaxis.[4]

The prophylactic use of oral or intravenous antibiotics has been recommended in several consensus guidelines. The recommended drugs are mainly oral quinolones (norfloxacin 400 mg b.i.d. for 7 days) or intravenous cephalosporins (ceftriaxone 1 g/day for 7 days).[5] A previous systematic review[6] assessed the benefits and harms of antibiotic prophylaxis in patients with cirrhosis and gastrointestinal haemorrhage. Since then, new trials have become available providing novel evidence about the effects of this intervention.

The aim of this systematic review was to assess the benefits and harms of antibiotic prophylaxis in cirrhotic patients with upper gastrointestinal bleeding. Specifically this review was designed to: a) compare all-cause mortality and infection mortality between cirrhotic patients with gastrointestinal bleeding receiving antibiotic prophylaxis or no intervention/placebo; and b) compare the frequency of bacterial infections in patients with gastrointestinal bleeding receiving antibiotic prophylaxis vs. no intervention/placebo.

## METHODS

### Eligibility criteria

This review included randomised clinical trials comparing different types of antibiotic therapy against no intervention, placebo, or another antibiotic, in the prophylaxis of bacterial infections in cirrhotic patients with upper gastrointestinal bleeding. Trials were included irrespective of publication status, language, or blinding.

### Outcomes

The primary outcomes considered in this review were: number of deaths (overall and associated with bacterial infections); and number of patients that developed bacterial infections. Secondary outcomes were: number of patients who dropped out from the trial after randomisation; number of patients with rebleeding, and number of days of hospitalisation.

### Data sources and searches

Relevant randomised trials were identified by searching The Cochrane Hepato-Biliary Group Controlled Trials Register, the Cochrane Central Register of Controlled Trials (Issue 2, 2010) in The Cochrane Library, MEDLINE (1950 to 21 June 2010), EMBASE (1980 to 21 June 2010) and Science Citation Index EXPANDED (1945 to 21 June 2010).[7] Search strategies and time span of the searches are provided in Table S1.

The reference list from all identified studies was inspected for more trials. Moreover, the first or corresponding author of each included trial, as well as researchers active in the field, were contacted for information regarding unpublished trials and additional information on their own trial.

### Study selection and data collection

Three authors (NC, FT, TB) independently inspected each identified reference and applied the inclusion criteria. For potentially relevant articles, or in cases of disagreement between the reviewers, the full text article was obtained and inspected independently. If necessary the original authors were contacted and, in the event of no reply, MU or KSW reviewed the article to solve the disagreement.

Two authors (NC and TB) independently extracted the data from included trials. In case of disagreement between the two authors, a third author (FT) extracted the data. Data extraction was discussed, decisions documented, and, when necessary, the authors of the original studies were contacted for clarification.

### Methodological quality assessment

The risk of bias was assessed following the instructions given in the Cochrane Handbook for Systematic Reviews of Interventions.[8] The methodological quality of the trials was assessed based on sequence generation, allocation concealment, blinding of outcome assessors, incomplete outcome data and early stopping for benefit.

### Data synthesis and analysis

Relative risk (RR) and its respective 95% CI were used as summary measure of association for trials with dichotomous primary outcomes. Continuous data were analysed calculating mean differences (MD) and 95% CI between trials evaluating antibiotic prophylaxis against no

intervention or placebo, and trials comparing different antibiotic regimens.

Heterogeneity of effects across trials was evaluated by visual inspection of the forest plots and $\chi^2$ and $I^2$ tests for heterogeneity.[8] Statistical heterogeneity was defined as a $P$ value $\leq 0.10$ ($\chi^2$) or $I^2 > 25\%$. A funnel plot estimating the precision of trials (plot of logarithm of the RR against the sample size) was examined to evaluate the potential for publication bias.

We analysed data using both fixed and random-effects models. When both models produced similar estimates, the fixed-effect result was reported. To examine the influence of drop-outs, we performed both worst-best-case (assigning bad outcomes to all of the missing experimental group patients and good outcomes to all of the missing control group patients) and best-worst-case (assigning good outcomes to all of the missing experimental group patients and bad outcomes to all the missing control group patients) analyses.

To assess the reliability of the meta-analyses on mortality, mortality from bacterial infections and bacterial infections, the required information size (RIS) was calculated by trial sequential analysis (TSA). We assumed an average event proportion of 22%, 5% and 36% in the control group of the three analyses; a 20% relative risk reduction of the experimental intervention and statistical error levels of 5% alpha and 20% beta (80% power) respectively. Whenever the cumulative information size in the meta-analysis was smaller than the RIS, the threshold to maintain statistical significance was calculated with the O'Brien-Fleming boundaries.[9]

For the statistical analyses, we used RevMan Analyses.[10] To compare the RR from different antibiotic groups and detect differences among the antibiotics tested vs. no intervention or placebo, a test for interaction was calculated.[11]

## RESULTS

### Study characteristics

Seventeen trials were included (1891 participants) for analyses[12–28]; Figure 1 shows the study screening workflow. Table 1 presents twelve trials comparing antibiotic prophylaxis using quinolones (five trials), quinolones plus beta-lactams (two trials), cephalosporins (three trials), carbapenems (one trial) and non-absorbable antibiotics (one trial) against no intervention or placebo.[12–18, 20, 23–25, 28] Head-to-head antibiotic comparisons were explored in five trials (Table 1),[19, 21, 22, 26, 27] as follows: combination of antibiotics vs. a single antibiotic,[21] two antibiotics from the same group,[19, 22] and different groups of antibiotics in each intervention group.[26, 27]

### Effects of interventions

The effect of antibiotic prophylaxis on all-cause mortality was significant (RR 0.79, 95% CI 0.63–0.98) (Figure 2). This association was sensitive to the drop-out rate, as revealed by the best-worst-case (RR 0.48, 95% CI 0.38–

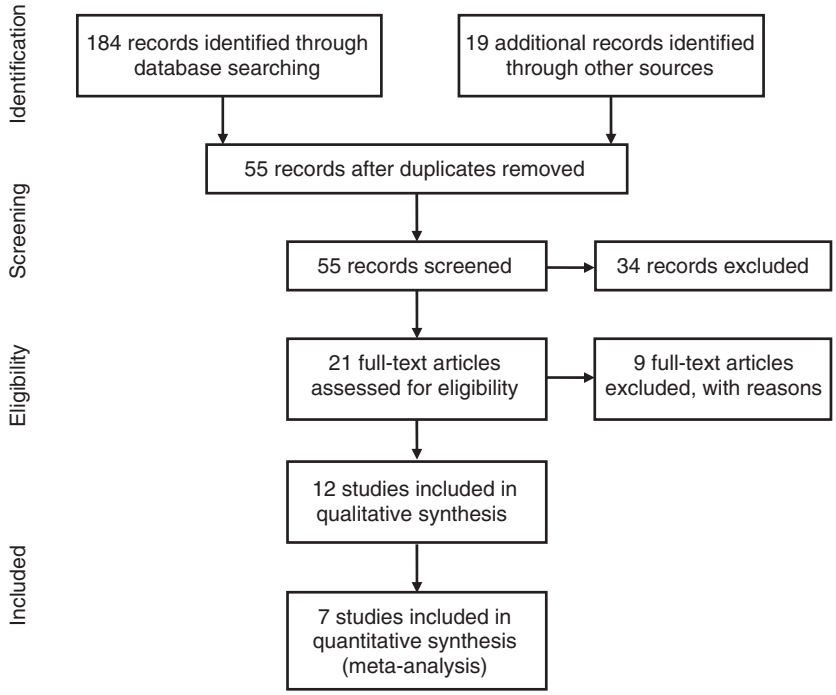


**Figure 1** | Study screening flow chart.

**Table 1** | Characteristics of included trials

| Study | Country | Intervention | Control | Outcome |
|---|---|---|---|---|
| Trials comparing with placebo or no intervention | | | | |
| Rimola *et al.*[12] | Spain | Group Ia – oral gentamicin (200 mg) + vancomycin (500 mg) + nystatin ($10^6$ UI) every 6 h, until 2 days after cessation of haemorrhage. Group Ib – neomycin (1 g) + colistin ($1.5 \times 10^6$ UI) + nystatin ($10^6$ UI) every 6 h, until 2 days safter cessation of haemorrhage. | No antibiotic prophylaxis | Bacterial infections |
| Soriano *et al.*[13] | Spain | Oral norfloxacin 800 mg/day during 7 days. | No antibiotic prophylaxis | Bacterial infections |
| Rolando *et al.*[14] | UK | Intravenous imipenem + cilastin, 500 mg before and after the sclerotherapy. | Intravenous dextrose-saline solution | Bacterial infections |
| Selby *et al.*[16] | Australia | Intravenous cefotaxime, 1 g immediately before sclerotherapy. | No antibiotic prophylaxis | Bacterial infections |
| Blaise *et al.*[15] | France | Intravenous + oral ofloxacin, 400 mg/day, 10 days; amoxicillin + clavulanic acid (bolus, 1 g) before each endoscopy procedure. | No antibiotic prophylaxis | Bacterial infections |
| Pauwels *et al.*[17] | France | Intravenous + oral ciprofloxacin 400 mg/day, amoxicillin-clavulanic acid 3 g/day, until 3 days after cessation of haemorrhage. | No antibiotic prophylaxis | Bacterial infections |
| Zacharof *et al.*[18] | Greece | Oral ciprofloxacin 500 mg/day during 7 days. | No antibiotic prophylaxis | Bacterial infections |
| Hsieh *et al.*[20] | Taiwan | Oral ciprofloxacin, 1 g/day, 7 days. | Placebo | Bacterial infections |
| Hong *et al.*[23] | Korea | Intravenous ciprofloxacin 200 mg b.d. for 3 days. | No antibiotic prophylaxis | Bacterial infections |
| Lin *et al.*[24] | Taiwan | Intravenous cefazolin 1 g t.d.s. during 3 days and then shift to oral cephalexin 500 mg q.d.s. for 4 days. | No antibiotic prophylaxis | Bacterial infections |
| Hou *et al.*[25] | Taiwan | Intravenous ofloxacin 200 mg b.d. for 2 days followed by oral ofloxacin 200 mg b.d. for 5 days. | No antibiotic prophylaxis | Rebleeding |
| Jun *et al.*[28] | Korea | Intravenous cefotaxime 2 g t.d.s. for 7 days. | No antibiotic prophylaxis | Rebleeding rate |
| Trials comparing with another antibiotic regimen | | | | |
| Sabat *et al.*[21] | Spain | Oral norfloxacin 800 mg/day, during 7 days plus intravenous ceftriaxone 2 g/day the first 3 days. | Oral norfloxacin 800 mg/day, 7 days | Bacterial infections |
| Spanish Group[19] | Spain | Oral norfloxacin, 800 mg/day, 5 days. | Oral ofloxacin, 400 mg/day, 5 days | Bacterial infections |
| Gulberg *et al.*[22] | Germany | Intravenous ceftriaxone, 1 g, single dose before TIPS. | Intravenous ceftriaxone, 2 g, single dose before TIPS | Bacterial infections |
| Lata *et al.*[26] | Czech Republic | Intravenous ampicillin/sulbactam 1.5 g b.d. for 7 days. | Oral or through nasogastric tube norfloxacin 400 mg b.d. for 7 days | Early and late mortality |
| Fernandez *et al.*[27] | Spain | Intravenous ceftriaxone 1 g/day for 7 days. | Oral norfloxacin 400 mg b.d. for 7 days | Bacterial infections |

0.60) and worst-best-case analyses (RR 1.45, 95% CI 1.04–2.02). The TSA showed a trend towards beneficial effects of the intervention to reduce mortality, but the cumulative Z-score did not cross the O'Brien-Fleming boundaries (data not shown).

Antibiotic prophylaxis was associated with a significant decrease in mortality from bacterial infections (RR 0.43, 95% CI 0.19–0.97) (Figure 3). The sensitivity analysis showed this estimation could have been biased by differential drop-out rates (worst-best-case analysis RR 3.30, 95% CI 1.43–7.62; best-worst-case analysis RR 0.14, 95% CI 0.06–0.31). The TSA demonstrated that the few number of trials included in the analysis were not enough to conclude a beneficial effect of prophylaxis over mortality from bacterial infections (data not shown).

Antibiotic prophylaxis significantly reduced bacterial infections when all trials with confirmed bacterial infections were considered (RR 0.35, 95% CI 0.26–0.47) (Figure 4a). Although heterogeneity of effects across trials was detected, effect estimators remained statistically significant with either fixed or random effects models, strengthening the evidence for the proposed effect. Estimators for bacterial infections were not affected by the sensitivity analysis (worst-best-case analysis RR 0.70, 95% CI 0.57–0.86; best-worst-case analysis RR 0.27, 95% CI 0.17–0.45), also, the TSA showed significant benefit of antibiotic prophylaxis over no intervention or placebo (Figure 4b).

Considering specific groups of infections, bacteraemia was reported in nine trials with a significant risk reduction in patients under antibiotic prophylaxis (RR 0.25, 95% CI 0.15–0.40). Similarly, other infectious outcomes were significantly reduced with the use of antibiotic prophylaxis: pneumonia in nine trials (RR 0.45, 95% CI 0.27–0.75), spontaneous bacterial peritonitis in eight trials (RR 0.29, 95% CI 0.15–0.57) and

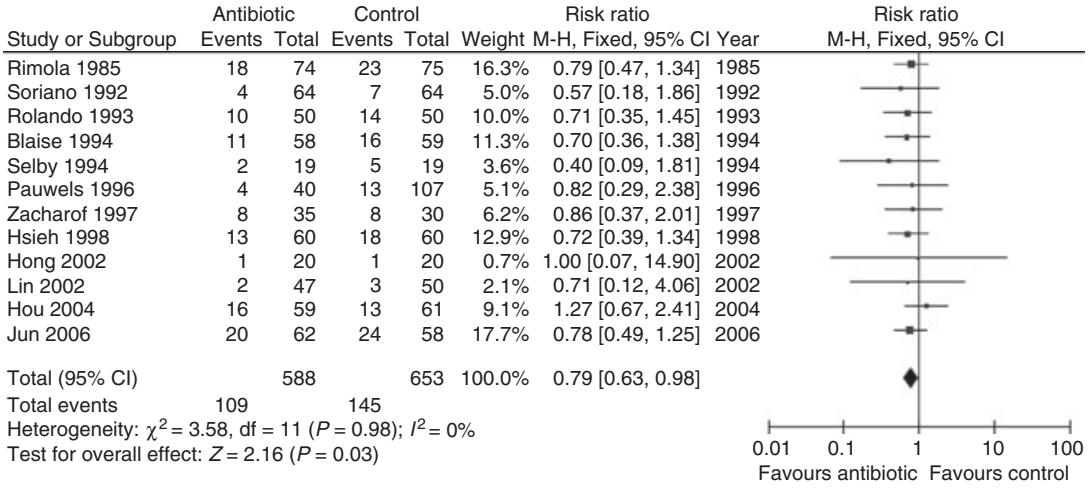


**Figure 2** | Forest plot of comparison: antibiotic vs. placebo/no intervention. Outcome: overall mortality.

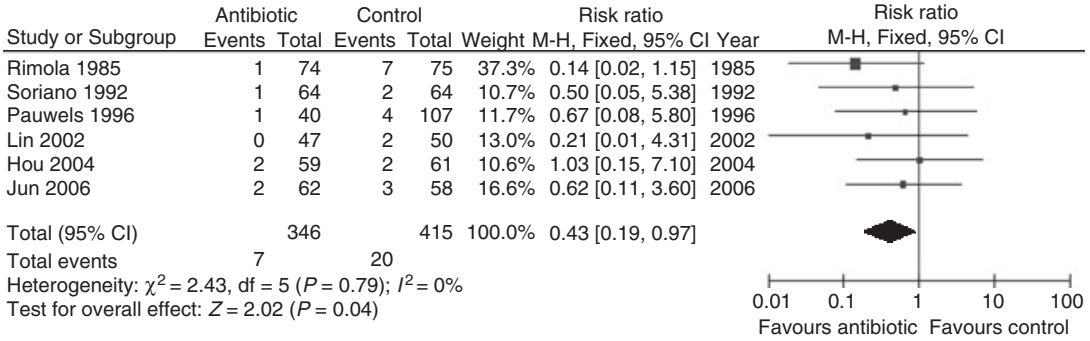


**Figure 3** | Forest plot of comparison: antibiotic vs. placebo/no intervention. Outcome: mortality due to bacterial infections.

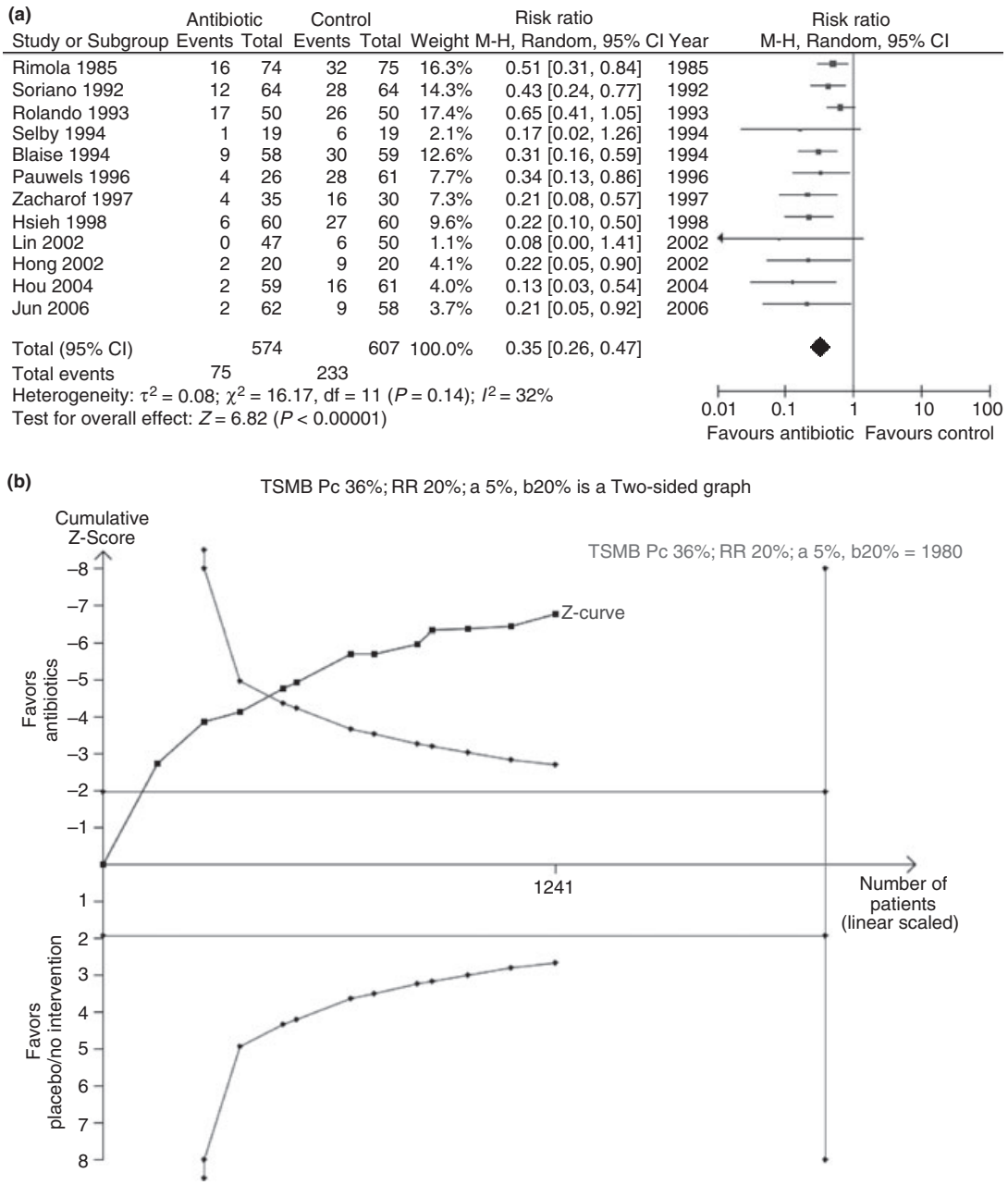


**Figure 4** | Forest plot of comparison: antibiotic vs. placebo/no intervention. Outcome: bacterial infections (Panel a). O'Brien-Fleming monitoring boundaries for assessing statistical significance for bacterial infections (Panel b). The solid curve presents the cumulative meta-analysis test-score and the inward sloping curves present the adjusted threshold for statistical significance – the two-sided O'Brien-Fleming boundaries.

urinary tract infections in nine trials (RR 0.23, 95% CI 0.13–0.41).

All antibiotics tested provided a beneficial effect over bacterial infections, although the protective effect was stronger with cephalosporins (RR 0.16, 95% CI 0.05–0.48), quinolones (RR 0.27, 95% CI 0.18–0.39), and quinolones plus beta-lactams (RR 0.38, 95% CI 0.23–0.62), than with other antibiotics (RR 0.57, 95% CI 0.41–0.81), compared with placebo or no intervention (Figure 5). However, the test for interaction demonstrated that only the group of 'other antibiotics' significantly differed from all other drugs. No significant difference between quinolones and cephalosporins was observed. In the head-to-head antibiotic comparison trials no significant differences between regimens were observed for the outcomes under study (Table 2).

A significant reduction in overall rebleeding episodes was observed among patients under antibiotic prophylaxis (RR 0.53, 95% CI 0.38–0.74), also, rebleeding after up to 7 days of follow-up was significantly reduced (RR 0.24, 95% CI 0.12–0.50).

Trials evaluating hospitalisation length showed patients receiving antibiotic prophylaxis tended to have shorter hospital stays (MD −1.91 days, 95% CI −3.80 to −0.02), however, this finding was not replicated in length of stay in the intensive care unit (MD −0.27 days, 95% CI −1.55–1.00).

## Quality of the evidence

This review included 1891 cirrhotic patients with upper gastrointestinal bleeding; 1241 of them participated in randomised trials comparing antibiotic prophylaxis vs. no intervention or placebo, and the remaining 650 participants in trials comparing different antibiotic prophylactic regimens. All trials presented methodological weaknesses and should be considered at risk of bias. Lack of blinding and lack of proper sample size calculations were the most common sources of bias (Table 3). Despite that the primary and secondary outcomes were included in the final analysis it is clear that the absence of mortality for bacterial infections, a clear and available outcome in the trials included could be considered an important source of bias.

The manuscripts included did not report adverse events, including resistance patterns.

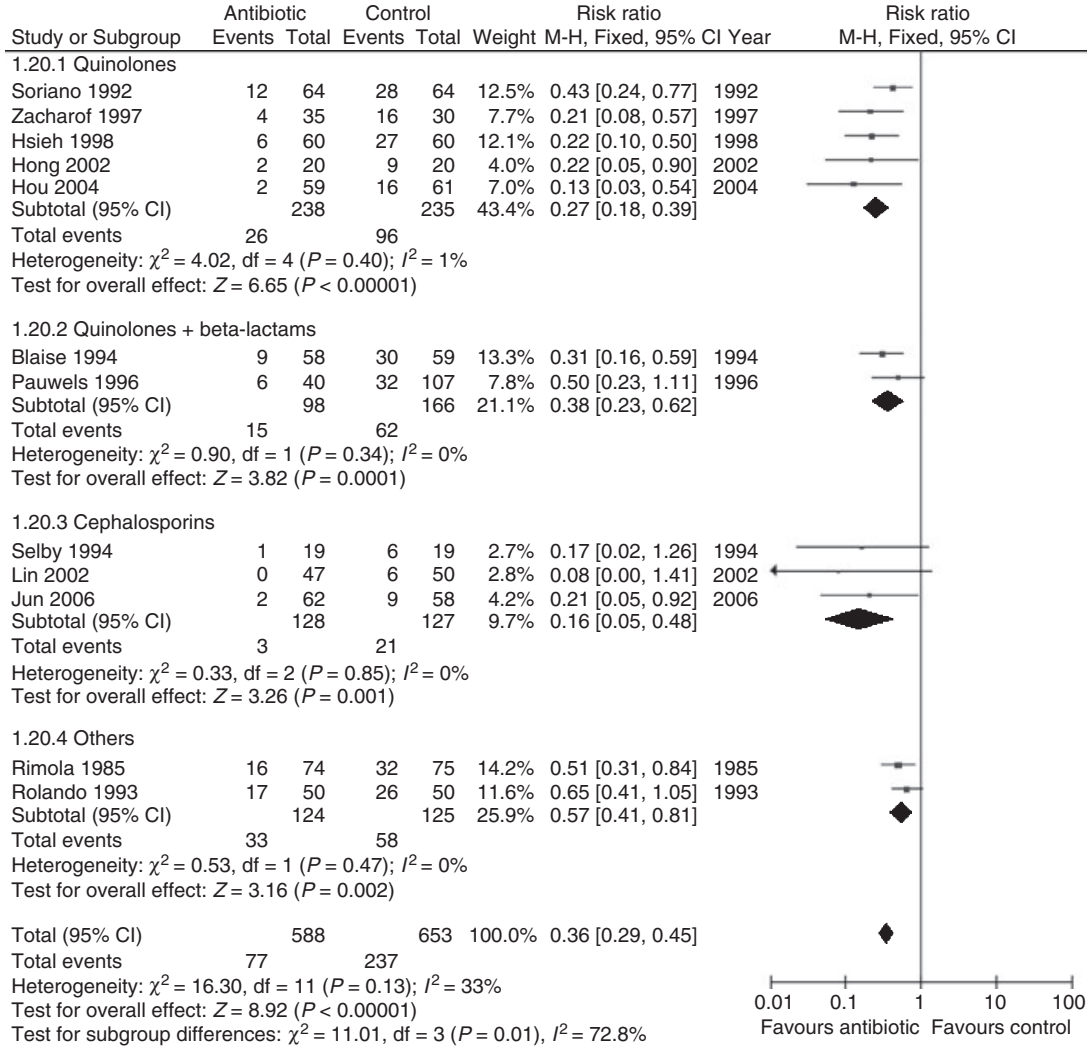


**Figure 5** | Forest plot of comparison: antibiotic vs. placebo/no intervention. Outcome: bacterial infections according to the antibiotic used.

**Table 2** | Data on trials comparing head-to-head two different regimens of antibiotic prophylaxis

| Author | Outcome | Experimental (*n*/*N*) | Control (*n*/*N*) | Relative risk | 95% CI |
|---|---|---|---|---|---|
| Sabat *et al.*[21] | Mortality | Norfloxacin + ceftriaxone (1/24) | Norfloxacin (2/22) | 0.46 | 0.04–4.71 |
| Sabat *et al.*[21] | Bacterial infections | Norfloxacin + ceftriaxone (3/24) | Norfloxacin (4/22) | 0.69 | 0.17–2.73 |
| Sabat *et al.*[21] | Cost | Norfloxacin + ceftriaxone – US $99.3–220.1 | Norfloxacin – US $1.9–745.5 | – | – |
| Sabat *et al.*[21] | Drop-outs | Norfloxacin + ceftriaxone (4/28) | Norfloxacin (6/28) | 0.67 | 0.21–2.11 |
| Gulberg *et al.*[22] | Mortality | Ceftriaxone 1 g (0/40) | Ceftriaxone 2 g (0/42) | Risk difference: 0.00 | −0.05–0.05 |
| Gulberg *et al.*[22] | Bacterial infections | Ceftriaxone 1 g (1/40) | Ceftriaxone 2 g (1/42) | 1.05 | 0.11–9.80 |
| Spanish Group[19] | Bacterial infections (proven) | Norfloxacin 800 mg (26/183) | Ofloxacin 400 mg (27/182) | 0.96 | 0.58–1.58 |
| Spanish Group[19] | Bacterial infections (suspected) | Norfloxacin 800 mg (51/183) | Ofloxacin 400 mg (53/182) | 0.96 | 0.69–1.32 |
| Lata *et al.*[26] | Mortality | Ampicillin and sulbactam 3 g (12/21) | Norfloxacin 800 mg (7/25) | 2.04 | 0.98–4.23 |
| Fernandez *et al.*[27] | Mortality | Ceftriaxone 1 g (8/54) | Norfloxacin 800 mg (6/57) | 1.41 | 0.52–3.79 |
| Fernandez *et al.*[27] | Mortality from bacterial infections | Ceftriaxone 1 g (1/54) | Norfloxacin 800 mg (1/57) | 1.06 | 0.07–16.46 |
| Fernandez *et al.*[27] | Bacterial infections | Ceftriaxone 1 g (6/54) | Norfloxacin 800 mg (5/57) | 1.27 | 0.41–3.94 |

## DISCUSSION

This review aimed to evaluate the effects of antibiotic prophylaxis over bacterial infections and mortality in cirrhotic patients with gastrointestinal bleeding. A significant reduction in bacterial infections was observed in patients receiving antibiotic prophylaxis as reported previously.[29] Also, although still not yet overwhelming, antibiotic prophylaxis was associated with reduced all-cause mortality, bacterial infection mortality, incidence of rebleeding events and length of hospitalisation.

This systematic review is an update of a systematic review and meta-analysis published in 2002.[6] The inclusion of new trials did not modify a previously observed beneficial effect of antibiotic prophylaxis on all-cause mortality and bacterial infections. New clinically relevant outcomes such as rebleeding and hospitalisation length were also included. Both rebleeding episodes and hospitalisation length were significantly reduced with antibiotic prophylaxis, although no association was observed with the time spent in critical care.

The evolution of the antibiotic prophylaxis goes from non-absorbable antibiotics, to quinolones, and, more recently, to cephalosporins. In the most recent update from the Baveno V scientific committee suggests as an area of further study the best antibiotic treatment.[30] Studies comparing antibiotic regimens against placebo or no intervention provided no solid evidence to prefer one antibiotic regimen over the other. A similar finding was observed in trials conducting head to head antibiotic comparisons. In general prophylaxis benefits were observed indistinctly of the antibiotic used, therefore, no specific regimen can be recommended over another, and antibiotic selection should be made considering local conditions such as bacterial resistance profile and treatment cost. Use of quinolones was first explored by Soriano *et al.*[13] and quinolones have been broadly used since then, despite rising concerns of a potential reduction of their effects due to bacterial resistance. However, considering that bacterial resistance pattern vary by location, use of quinolones for antibiotic prophylaxis will have to be assessed in specific local settings. The available information does not allow establishing any conclusion about the best option for antibiotic prophylaxis.

The current evidence to support antibiotic prophylaxis is based on twelve randomised trials and, except for

**Table 3** | Risk of bias summary, review authors' judgments about each risk of bias item for each included study

| Author | Sequence generation | Allocation concealment | Blinding | Incomplete outcome | Selective reporting | Other bias | Intention to treat | Sample calculation |
|---|---|---|---|---|---|---|---|---|
| Rimola *et al.*[12] | + | + | – | – | + | – | – | – |
| Soriano *et al.*[13] | + | ? | – | + | + | + | – | – |
| Rolando *et al.*[14] | + | + | – | + | + | ? | – | – |
| Selby *et al.*[16] | + | + | – | + | + | ? | – | – |
| Pauwels *et al.*[17] | + | ? | – | + | + | + | – | – |
| Zacharof *et al.*[18] | + | + | – | + | ? | ? | ? | ? |
| Hsieh *et al.*[20] | ? | ? | ? | + | + | + | + | – |
| Sabat *et al.*[21] | ? | ? | – | + | + | – | – | ? |
| Spanish Group[19] | ? | ? | ? | ? | ? | ? | ? | ? |
| Gulberg *et al.*[22] | ? | ? | – | + | + | – | ? | – |
| Hong *et al.*[23] | ? | ? | – | ? | + | ? | ? | ? |
| Lin *et al.*[24] | ? | ? | – | + | + | + | – | – |
| Blaise *et al.*[15] | ? | ? | – | + | + | + | – | – |
| Hou *et al.*[25] | + | ? | – | + | + | + | – | + |
| Lata *et al.*[26] | + | ? | – | + | + | + | ? | – |
| Fernandez *et al.*[27] | + | ? | – | + | + | + | – | + |
| Jun *et al.*[28] | + | + | – | – | + | + | – | + |

America and Africa, the intervention has been assessed in heterogeneous populations, providing external validity to this review. The effects observed were more robust for prevention of bacterial infections than for mortality reduction, which could be explained by the fact that all trials included were designed and powered to evaluate this outcome. The bias associated with the lack of information regarding mortality for bacterial infections is not a minor issue. This bias limits the strength of the conclusion about the beneficial effects of antibiotics in this outcome, and in consequence it is not clear exactly how the beneficial effect on overall mortality is reached. The logical argument indicates that the most important benefit from an antibiotic intervention must be related with their effects on infections. However, the indirect effects of antibiotics[31] could influence the overall mortality, but this has not been properly addressed.

Trials analysing rebleeding rate and hospitalisation length are still scarce, thus, caution should be exerted when interpreting the results.

In conclusion, this up-dated systematic review and meta-analysis, enhances the beneficial effects of antibiotic prophylaxis in patients with cirrhosis and gastrointestinal bleeding. Novel, clinically significant outcomes were included among the benefits from antibiotic prophylaxis. This increases the size of treatment effect, promoting this intervention as the standard of care. However, some benefits remains unclear and the risks are not yet properly assessed.

## ACKNOWLEDGEMENTS

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## SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Search strategy and time span.

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En esta revisión sistemática y meta-análisis evaluamos la evidencia más actual en relación con el uso profiláctico de antibióticos en pacientes cirróticos con sangrado gastrointestinal. Nuestros resultados apoyan la utilidad de los antibióticos en este escenario en razón de que reducen significativamente las infecciones bacterianas y reducen la mortalidad en general (independientemente de la causa), la mortalidad por infecciones bacterianas, reducen la recurrencia de sangrados y disminuyen la estancia hospitalaria.

**Citas recibidas a este trabajo: 9**


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BRIEF ARTICLE

# Vigorous, but differential mononuclear cell response of cirrhotic patients to bacterial ligands

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## Abstract

**AIM:** To study the role of gram-positive and gram-negative bacteria in the pathogenesis of liver injury, specifically the activation of inflammatory mediators.

**METHODS:** Peripheral blood mononuclear cells of 20 out-patients were studied, 10 of them with cirrhosis. Peripheral blood mononuclear cells were isolated and exposed to lipopolysaccharide or lipoteichoic acid. CD14, Toll-like receptor 2 and 4 expression was determined by flow cytometry, and tumor necrosis factor (TNF) α, interleukin (IL)-1β, IL-6, IL-12 and IL-10 secretion in supernatants was determined by ELISA.

**RESULTS:** Higher CD14, Toll-like receptor 2 and 4 expression was observed in peripheral blood mononuclear cells from cirrhotic patients, ($P < 0.01$, $P < 0.006$, $P < 0.111$) respectively. Lipopolysaccharide and lipoteichoic acid induced a further increase in CD14 expression ($P < 0.111$ lipopolysaccharide, $P < 0.013$ lipoteichoic acid), and a decrease in Toll-like receptor 2 ($P < 0.008$ lipopolysaccharide, $P < 0.008$ lipoteichoic acid) and Toll-like receptor 4 ($P < 0.008$ lipopolysaccharide, $P < 0.028$ lipoteichoic acid) expression. With the exception of TNFα, absolute cytokine secretion of peripheral blood mononuclear cells was lower in cirrhotic patients under non-exposure conditions ($P < 0.070$ IL-6, $P < 0.009$ IL-1β, $P < 0.022$ IL-12). Once exposed to lipopolysaccharide or lipoteichoic acid, absolute cytokine secretion of peripheral blood mononuclear cells was similar in cirrhotic and non-cirrhotic patients, determining a more vigorous response in the former ($P < 0.005$ TNFα, IL-1β, IL-6, IL-2 and IL-10 lipopolysaccharide; $P < 0.037$ TNFα; $P < 0.006$ IL-1β; $P < 0.005$ IL-6; $P < 0.007$ IL-12; $P < 0.014$ IL-10 lipoteichoic acid). Response of peripheral blood mononuclear cells was more intense after lipopolysaccharide than after lipoteichoic acid exposure.

**CONCLUSION:** Peripheral blood mononuclear cells of cirrhotic patients are able to respond to a sudden bacterial ligand exposure, particularly lipopolysaccharide, suggesting that immune regulation mechanisms are still present.

**Key words:** Liver cirrhosis; Toll-like receptors; Cytokines; Lipopolysaccharide; Lipoteichoic acid

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## INTRODUCTION

Patients with cirrhosis frequently present with intestinal bacterial overgrowth of both gram-negative and gram-positive bacteria. Coexisting increased intestinal permeability facilitates bacterial translocation into the portal vein[1]. The resulting bacteremia and endotoxemia can not be efficiently cleared by the injured liver[2], leading to a rise of systemic proinflammatory cytokines[3]. This is thought to aggravate the underlying liver damage. The role of gram-negative bacteria in the pathogenesis of liver injury has been extensively studied. As to gram-positive bacteria, a similar deleterious role has been proposed[4], but still remains to be proven.

It is known that bacterial cell wall products, such as lipopolysaccharide (LPS), lipoteichoic acid (LTA) and peptidoglycan (PGN) fragments, trigger monocyte expression of many inflammatory cytokines. LPS, also known as endotoxin, a major constituent of the outer membrane of gram-negative bacteria, elicits an immune reaction which is responsible for many of the harmful effects seen in septic shock patients. LPS binds to the LPS-binding protein (LBP), a member of a binding and transport protein family. It requires either mCD14 or sCD14 receptors to be transferred to the toll-like receptor 4 (TLR4), a transmembrane signaling receptor, and translocated into the hydrophobic pocket of myeloid differentiation factor-2 (MD-2)[5]. This signaling pathway activates a variety of transcription factors such as nuclear factor (NF)-κB (p50/p65) and AP-1 (c-Fos/c-Jun), which induce the production of many inflammatory mediators[6].

Nowadays, it has become clear that LPS can not reproduce all clinical features of sepsis. This emphasizes the participation of other contributing factors. Gram-positive bacteria, which lack LPS, are responsible today for a substantial part of sepsis incidence. The rapid transmission and acquisition of antibiotic-resistance genes among gram-positive bacteria, and their propensity to adhere and persist on vascular catheter surfaces and other implantable medical devices have contributed to an increasing incidence of gram-positive pathogens as a cause of sepsis[7]. The major wall components of gram-positive bacteria, LTA and PGN, are thought to contribute to the development of sepsis, septic shock[8] and multiple organ dysfunction syndrome (MODS)[9]. Like LPS, LTA can interact with CD14 to initiate signal transduction pathways that lead to NF-κB activation[10]. It has been observed recently, that LTA is recognized by TLR2, which heterodimerises with either TLR1 or TLR6[11,12]. Activation of the TLR2/6 heterodimer is greatly facilitated by CD36 in a similar way as TLR4 by CD14[13].

This study compares, in cirrhotic and non-cirrhotic patients, the ability to activate inflammatory pathways of both gram-negative and gram-positive bacteria ligands. We therefore assessed the response of peripheral blood mononuclear cells (PBMC) of cirrhotic and non-cirrhotic patients to LPS and LTA exposure in terms of receptor expression (CD14, TLR2 and TLR4) and cytokine secretion [tumor necrosis factor (TNF) α, interleukin (IL)-1β, IL-6, IL-12 and IL-10].

**Table 1 Biochemical characteristics of non-cirrhotic and cirrhotic patients**

| | Non-Cirrhotic ($n$ = 10) | Cirrhotic ($n$ = 10) |
|---|---|---|
| Bilirubin (mg/dL) | 0.8 (0.6-1.2) | 1.2 (0.5-28.5) |
| Albumin (g/dL) | 4.0 (1.8-4.2) | 3.3 (1.2-4.1) |
| PT (sec/ctl) | 11.8 (9.7-15.3) | 11.6 (10.2-18.4) |
| ALT (IU/L) | 23 (15-61) | 32.5 (19-57) |
| AST (IU/L) | 23 (17-48) | 43 (28-180) |
| Alkaline phosphatase (IU/L) | 78 (56-204) | 145.5 (56-479) |

Data are expressed as median (minimum -maximum) values. PT: Prothrombin time; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

## MATERIALS AND METHODS

### Patients

Twenty out-patients were studied, ten of them with cirrhosis. Diagnosis of cirrhosis was supported clinically, by laboratory tests and ultrasound. Cirrhosis was due to alcohol in 4 patients, cryptogenic in 5, and due to portal thrombosis in 1. Child-Pugh classification was A in 5 patients, B in 3, and C in 2. Male:female ratio was 1:1 and the median age was 56.5 (36-79) years. Coexisting disorders were diabetes in 2 patients, hypertension in 1 and systemic sclerosis in 1. Laboratory tests are summarized in Table 1. Non-cirrhotic controls were patients with dyslipidemia (4), peptic ulcer disease (3), hypothyroidism (2), major depression (1), diabetes (1), hypertension (1), and achalasia (1). Their male:female ratio was 1:4 and median age 54.5 (41-75) years. At the time of inclusion, subjects neither had a concurrent infectious disorder, nor were receiving antibiotic or immune-modulating therapy. They all signed an informed consent before entry. The protocol of the study was approved by the Human Biomedical Research Committee of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán.

### Isolation and stimulation of PBMC

Peripheral blood mononuclear cells were used as experimental units, given that they represent well-suited low-cost proxy-measures of monocytic response[14]. Peripheral venous blood was collected with heparinized sterile pyrogen-free disposable syringes (Becton Dickinson). PBMC were isolated from blood samples on a lymphoprep gradient (Axis Shield). After washing, PBMC were adjusted to $10^6$ cells/mL in RPMI 1640 (Life Technologies, Invitrogen), and supplemented with 10% heat-inactivated fetal bovine serum (GIBCO, Invitrogen) and 1% penicillin-streptomycin 500 U/mL-500 μg/mL (GIBCO, Invitrogen). Then, $3 \times 10^6$ cells were plated on 2 mL media in 6-well round bottom tissue culture plates (NUNC). After stabilization at 37℃ and 5% $CO_2$, cells were stimulated (duplicate experiments) with either 0.1 μg/mL ultra-purified *Escherichia coli* endotoxin (Sigma Chemical Co.) or 0.1 μg/mL *Streptococcus faecalis* lipoteichoic acid (Sigma Chemical Co.). In order to establish the optimal concentration of activation, PBMC from blood donors were cultured with LPS or LTA at different concentrations such as 0.01, 0.1, 1 and 10 μg/mL and 0.1, 1.0, 10 and 20 pg/mL, respectively. Cultures were incubated for 24 h before supernatant harvest and TNFα concentration measurement. TNFα levels were found highest with a concentration of 0.1 pg/mL. Also, to establish the optimal time of activation, normal PBMC were cultured with 0.1 pg/mL of LPS or LTA, and supernatants harvested after 6, 24 and 48 h. TNFα levels were highest after 24 h (data not shown). We therefore used 0.1 pg/mL of LPS or LTA for a 24-h exposure. Supernatants were harvested after 24 h and stored at -70℃ until analysis.

### CD14, TLR2 and TLR4 expression

$5 \times 10^5$ freshly isolated or cultured PBMC were kept unexposed (NE), or were treated with LPS or LTA for 24 h. The expression of CD14, TLR2 or TLR4 was determined by flow cytometry. Briefly, treated PBMC were resuspended at $5 \times 10^5$ cells/mL in blocking buffer (PBS containing 2% FBS, 2% rabbit serum, 5 mM EDTA and 0.1% sodium azide) and incubated on ice for 30 min. Cell suspension was centrifuged and stained with fluorescein isothiocyanate (FITC)-conjugated anti-human CD14 (Santa Cruz Biotechnology), phycoeritrin (PE)-conjugated anti-human TLR2 (Santa Cruz Biotechnology), and PE-conjugated anti-human TLR4 (Santa Cruz Biotechnology). Isotype-matched nonbinding control goat anti-mouse $IgG_{2a}$ (Santa Cruz Biotechnology) was used. The cells were incubated for 15 min in the dark, washed twice with FACS buffer (PBS containing 2% FBS, 5 mmol/L EDTA and 0.1% sodium azide) and fixed with 4% paraformaldehide in PBS (pH 7.2) for 30 min and analyzed on an EPICS-ALTRA (Beckman-Coulter). A total of 20 000 events was obtained for each sample. Data were analyzed with WinMDI 2.8 software. CD14, TLR2 and TLR4 values were expressed as % fluorescence.

### Cytokine assays

After activation, cell-free culture supernatants were harvested and concentrations of TNFα, IL-1β, IL-6, IL-12 and IL-10 were measured by enzyme-linked immunosorbent assay (ELISA) (OptEIA™, BD Pharmingen, San Diego, CA) according to the manufacturer's instructions. Detection limits for each assay were 4 pg/mL for TNFα, IL-1β, IL-6, and IL-10, and 15 pg/mL for IL-12. In each patient, every test was run in duplicate.

Data are summarized as median (minimum and maximum) values. Taking the NE condition as reference, absolute and relative (%) differences were determined for LPS or LTA exposed PBMC of cirrhotic and non-cirrhotic patients. The Mann-Whitney test was used to analyze differences between cirrhotic and non-cirrhotic groups, and the Wilcoxon sign-rank test to analyze differences between exposure and non-exposure to LPS or LTA. A $P$ value < 0.05 was considered as statistically significant, and a $P < 0.10$ as tendency towards significance. The Stata v7 statistical package was used.

## RESULTS

### CD14, TLR2 and TLR4 expression

Expression of CD14, TLR2 and TLR4 by NE PBMC was higher in cirrhotic than non-cirrhotic patients. Median CD14 expression was 13.3% (8.9-34.6) *vs* 6.7% (3.5-27.5) ($P < 0.01$), median TLR2 expression was 9% (4.8-19.5) *vs* 4.8% (1.7-7.9) ($P < 0.006$), and median TLR4 expression was 26.9% (5.9-36.4) *vs* 8.5% (1.2-30) ($P < 0.111$), respectively. (Figure 1A-C) Non-exposure (NE), LPS or LTA exposure, bars represent median values.

After exposure to LPS, CD14 expression by PBMC of non-cirrhotic patients [5.6% (2-28.2)] was not significantly different from corresponding NE values [6.7% (3.5-27.5), NS], but TLR2 and TLR4 expressions were significantly lower [2% (1-6.5) *vs* 4.8% (1.7-7.9), $P < 0.047$, and 3.5% (0.9-26.1) *vs* 8.5% (1.2-30), $P < 0.028$]. PBMC of cirrhotic patients showed, after the same exposure, an increased CD14 expression [23.2% (3.2-48.5) *vs* 13.3% (8.9-34.6), $P < 0.111$], and significantly decreased TLR2 [4.9% (1.1-10.8) *vs* 9% (4.8-19.5), $P < 0.008$] and TLR4 [14.8% (1.2-32) *vs* 26.9% (5.9-36.4), $P < 0.008$] expression (Figure 1A-C). Taking the NE condition as 100% reference, the median relative difference in CD14 expression tended to be higher in cirrhotic than non-cirrhotic patients after LPS exposure ($P < 0.096$). As to TLR2 and TLR4 expression, LPS exposure induced a non-significant trend towards larger median relative differences in cirrhotic than non-cirrhotic patients. (Table 2)

LTA exposure did not affect significantly CD14 expression in non-cirrhotic patients [6.5% (3.6-26.9)] when compared to NE conditions [6.7% (3.5-27.5), NS], neither did it affect TLR2 [2.1% (1-8.2) *vs* 4.8% (1.7-7.9), NS] expression. TLR4 expression was, however, significantly decreased [2.7% (0.7-28.8) *vs* 8.5% (1.2-30), $P < 0.013$]. LTA challenged PBMC of cirrhotic patients showed sig-

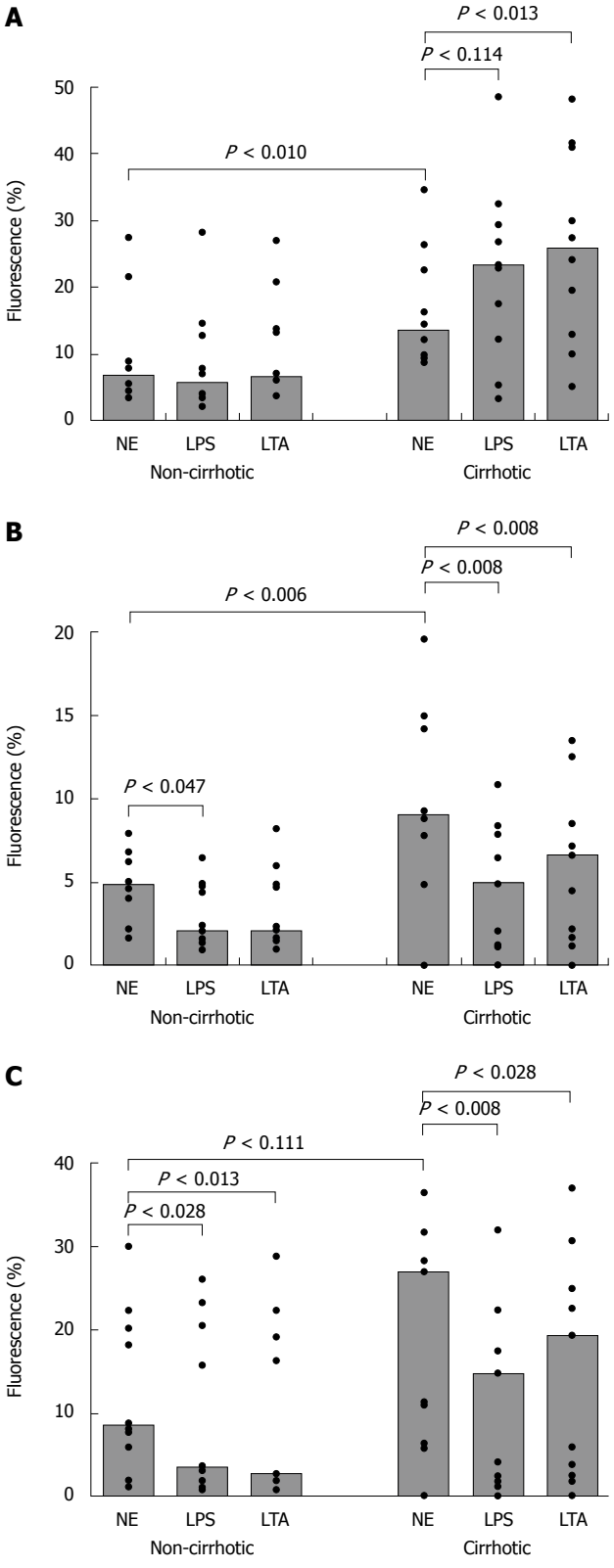


**Figure 1 Receptor expression from peripheral blood mononuclear cells of non-cirrhotic and cirrhotic patients under conditions of non-exposure, lipopolysaccharide or lipoteichoic acid exposure for CD14, toll-like receptor 2 and toll-like receptor 4 expression.** Bars represent median values. $P < 0.05$ denotes statistical significance and $P < 0.10$ denotes tendency to statistical significance. A: CD14 expression; B: TLR2 expression; C: TLR4 expression. NE: Non-exposure; LPS: Lipopolysaccharide; LTA: Lipoteichoic acid.

nificantly increased CD14 expression [25.7% (5-48.2) *vs* 13.3% (8.9-34.6), $P < 0.013$], and decreased TLR2 [6.6% (1.2-13.4) *vs* 9% (4.8-19.5), $P < 0.008$] and TLR4 [19.4% (1.9-37) *vs* 26.9% (5.9-36.4), $P < 0.028$] expression (Figure 1A-C). LTA induced median relative differences in CD14, TLR2 and TLR4 expression were similar to those induced by LPS (Table 2).

**Table 2 Median relative difference[1] in receptor expression and cytokine secretion by peripheral blood mononuclear cells of non-cirrhotic and cirrhotic patients after exposure to lipopolysaccharide and lipoteichoic acid**

| | | Non-cirrhotic $n = 10$ | Cirrhotic $n = 10$ | *P* value |
|---|---|---|---|---|
| Expression | | | | |
| CD14 | LPS | -9% | +39% | < 0.096[b] |
| | LTA | -3.50% | +55% | < 0.028[a] |
| TLR2 | LPS | -10% | -60% | < 0.121 |
| | LTA | 0% | -42% | < 0.289 |
| TLR4 | LPS | 30% | -53% | < 0.221 |
| | LTA | -19.50% | -29% | < 0.935 |
| Secretion | | | | |
| TNFα | LPS | +7400% | +8770% | < 0.940 |
| | LTA | +190% | +360% | < 0.970 |
| IL-1β | LPS | +70.50% | +1164% | < 0.019[a] |
| | LTA | -6% | +71% | < 0.049[a] |
| IL-6 | LPS | +91% | +319% | < 0.174 |
| | LTA | +125% | +246% | < 0.326 |
| IL-12 | LPS | +3324% | +6219% | < 0.151 |
| | LTA | +503% | +1786% | < 0.227 |
| IL-10 | LPS | +1768% | +5844% | < 0.364 |
| | LTA | +50% | +415% | < 0.571 |

[1]Difference with the non-exposure value (considered as the reference or 100%). A negative value reflects a decrease, whereas a positive value reflects an increase. [a]Denotes statistically significant ($P < 0.05$) differences between non-cirrhotic and cirrhotic patients. [b]Denotes tendency towards statistically significant ($P < 0.10$) differences between non-cirrhotic and cirrhotic patients. LPS: Lipopolysaccharide; LTA: Lipoteichoic acid; TLR: Toll-like receptor; IL: Interleukin; TNF: Tumor necrosis factor.

### *TNFα, IL-1β, IL-6, IL-12 and IL-10 secretion*

NE PBMC of non-cirrhotic *vs* cirrhotic patients secreted similar amounts of TNFα [⩽ 4 pg/mL (⩽ 4-143) *vs* ⩽ 4 pg/mL (⩽ 4-42), NS] and IL-10 [26 pg/mL (⩽ 4-275) *vs* 6 pg/mL (⩽ 4-72), NS]. Secretion of IL-6 tended to be higher in non-cirrhotic [401 pg/mL (12-1530)] than cirrhotic [168 pg/mL (5-459)], patients ($P < 0.070$). Secretion of IL-1β and IL-12 was significantly higher in non-cirrhotic [26 pg/mL (⩽ 4-159) and 19 pg/mL (⩽ 15-959)] than cirrhotic [⩽ 4 pg/mL (⩽ 4-10) and ⩽ 15 pg/mL (⩽ 15-38)] patients ($P < 0.009$ and $< 0.022$). (Figure 2A-E).

Taking NE values as reference [⩽ 4 pg/mL (⩽ 4-143) and ⩽ 4 pg/mL (⩽ 4-42)], LPS exposure triggered significant increases in TNFα secretion by both non-cirrhotic [443 pg/mL (52-658), $P < 0.005$] and cirrhotic [355 pg/mL (52-713), $P < 0.005$] PBMC. Similar increases were observed for IL-1β, IL-6, IL-12 and IL-10 secretion. Specifically, IL-1β PBMC secretion increased from NE values of 26 pg/mL (⩽ 4-159) in non-cirrhotic and ⩽ 4 pg/mL (⩽ 4-10) in cirrhotic patients, to 61 pg/mL (8-192) and 51 pg/mL (17-286) after LPS exposure, respectively ($P < 0.028$ and $< 0.005$). As for IL-6, secre-

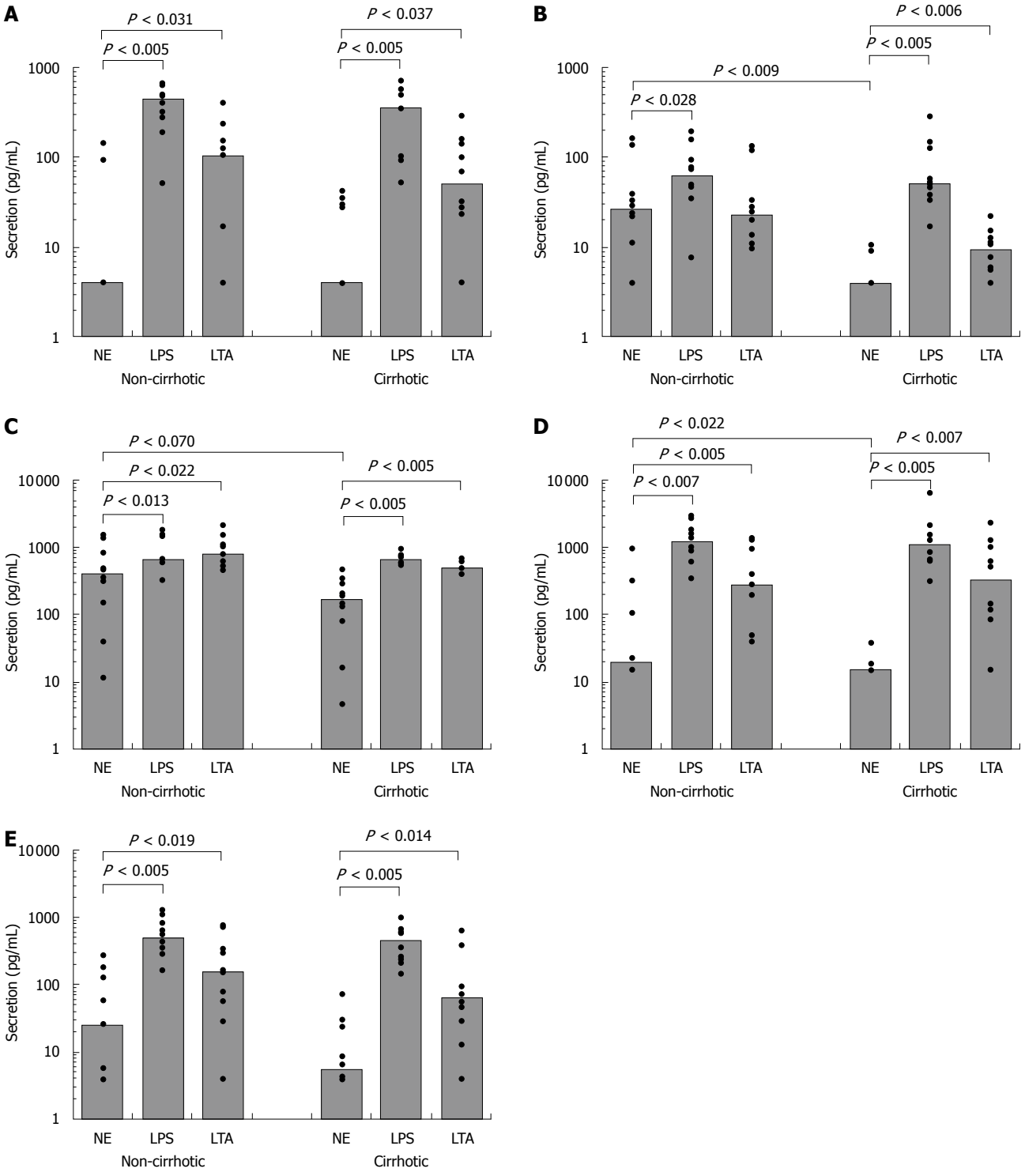


**Figure 2 Cytokine secretion from peripheral blood mononuclear cells of non-cirrhotic and cirrhotic patients under conditions of non-exposure, lipopolysaccharide or lipoteichoic acid exposure for tumor necrosis factor α, interleukin-1β, interleukin-6, interleukin-12 and interleukin-10 secretion**. Bars represent median values. $P < 0.05$ denotes statistical significance and $P < 0.10$ denotes tendency to statistical significance. A: Tumor necrosis factor α secretion; B: Interleukin (IL)-1β secretion; C: IL-6 secretion; D: IL-12 secretion; E: IL-10 secretion. NE: Non-exposure; LPS: Lipopolysaccharide; LTA: Lipoteichoic acid.

tion increased from NE values of 401 pg/mL (12-1530) and 168 pg/mL (5-459), to 645 pg/mL (325-1793) and 660 pg/mL (540-946), $P < 0.013$ and $< 0.005$. IL-2 secretion showed an increase from 19 pg/mL (≤ 15-959) and ≤ 15 pg/mL (≤ 15-38), to 1201 pg/mL (15-2850) and 1074 pg/mL (317-6397), $P < 0.007$ and $< 0.005$. IL-10 secretion was 26 pg/mL (≤ 4-275) and 6 pg/mL (≤ 4-72) under NE conditions, and 498 pg/mL (163-1292) and 464 pg/mL (146-1010) after LPS exposure, $P < 0.005$ and $< 0.005$. Median relative difference in cytokine secretion between LPS exposure and NE tended to be higher in cirrhotic than non-cirrhotic patients, reaching statistical

significance in IL-1β only ($P < 0.019$) (Table 2).

To a lesser degree than LPS, LTA exposure also induced increases in cytokine secretion. TNFα secreted by PBMC of non-cirrhotic and cirrhotic patients increased from NE values of ≤ 4 pg/mL (≤ 4-143) and ≤ 4 pg/mL (≤ 4-42), to 105 pg/mL (4-409) and 51 pg/mL (4-288), $P < 0.031$ and $< 0.037$. IL-1β secretion was 26 pg/mL (≤ 4-159) and ≤ 4 pg/mL (≤ 4-10) under NE conditions, and 23 pg/mL (10-133) and 9 pg/mL (4-22) after LTA exposure, NS and $P < 0.006$. IL-6 secretion increased from 401 pg/mL (12-1530) and 168 pg/mL (5-459), to 802 pg/mL (454-2155) and 509 pg/mL (397-705), $P < 0.022$ and $< 0.005$. IL-12 secretion increased from 19 pg/mL (≤ 15-959) and ≤ 15 pg/mL (≤ 15-38), to 275 pg/mL (40-1385) and 334 pg/mL (≤ 15-2339), $P < 0.005$ and $< 0.007$. IL-10 secretion increased from 26 pg/mL (≤ 4-275) and 6 pg/mL (≤ 4-72), to 157 pg/mL (≤ 4-756) and 64 pg/mL (≤ 4-638), $P < 0.019$ and $< 0.014$ (Figure 2A-E). Median LTA-induced relative differences in cytokine secretion tended to be more vigorous in cirrhotic than in non-cirrhotic patients, reaching statistical significance in IL-1β only ($P < 0.049$) (Table 2).

## DISCUSSION

In this study, higher PBMC CD14, TLR2 and TLR4 expression was observed in cirrhotic patients under NE and LPS/LTA exposure conditions. LPS and LTA exposure induced an increase in CD14 expression in cirrhotic patients, and a decrease in TLR2 and TLR4 expression in both non-cirrhotic and cirrhotic patients. With the exception of TNFα, PBMC absolute cytokine secretion was lower in cirrhotic patients under NE conditions. However, once exposed to LPS or LTA, cytokine secretion was similar in both non-cirrhotic and cirrhotic patients, determining a more vigorous response in the latter, as shown by the corresponding relative differences. As to LPS, and with the exception of IL-6 secretion, this bacterial ligand triggers a more vigorous cytokine response than LTA.

### *CD14, TLR2 and TLR4 expression*

Higher PBMC CD14 expression in cirrhotic patients under NE conditions reflects a state of hyperactivation, conditioned probably by a long-standing exposure to intestinal microorganisms and their products. This hyperactivation leads to vigorous reactions with any further bacterial stimuli [15]. It should be kept in mind that PBMC expression in our study is summarized as percentage of control baseline fluorescence conditions. In terms of the mean fluorescence intensity (MFI)[16-18], no significant differences in CD14, TLR2 or TLR4 expression among cirrhotic and non-cirrhotic PBMC before and after exposure to LPS and LTA were observed (data not shown). This means that the herein reported differences in PBMC expression reflect differences in the number of activated cells, not in the amount of antibody bound per cell.

Chronic increase in circulating LPS, and the resulting state of PBMC hyperactivation has been associated to low levels of high-density lipoprotein (HDL), a well-known complication of cirrhosis. HDL is able to bind LPS and neutralize its bioactivity. HDL can also down-regulate monocyte CD14 expression, and has other anti-inflammatory properties[19]. Low HDL levels could explain the increased CD14 expression observed in PBMC of our cirrhotic patients under both NE and exposed conditions.

As to LTA, this ligand relies, at least in part, on CD14 to initiate signal transduction pathways[10,20]. It has been shown recently, that CD14 expression enhances markedly LTA binding to plasma cell membranes[21]. It seems, therefore, that increased CD14 expression in cirrhosis is due to high circulating levels of both LPS and LTA. Increased circulating levels of LPS and proinflammatory cytokines have been documented in patients with chronic liver disease, even in the absence of infection. However, no significant correlation between LPS and these inflammatory mediators has been shown, raising the possibility that other agents, besides LPS, may play a role. Recent studies on TLR expression in cirrhotic patients show that this might be in fact true. TLR4, in the presence of LPS, triggers the signal transduction that leads to TNFα production. When PGN and LTA are present, TLR2 is required for signaling and activation of the inflammatory cascade. Recently, PBMC expression of TLR2, but not TLR4 was shown to correlate significantly with circulating levels of both TNFα and anti-inflammatory soluble TNF receptors. These findings suggest that gram-positive microbial stimuli might be important in the proinflammatory state of chronic liver disease. If proven true, this would contraindicate the use of probiotic agents, such as gram-positive lactobacilli, in cirrhotic patients. Current evidence, however, shows that probiotic use is associated with a significant increase of fecal lactobacilli and a decrease of potentially pathogenic gram-positive and gram-negative bacterial species. Probiotics reverse bacterial overgrowth and improve minimal hepatic encephalopathy. They improve the Child-Pugh class at the expense of serum bilirubin, albumin and prothrombin. Also, serial ALT levels show a significantly reduced hepatic necroinflammatory activity, suggesting that probiotics can protect against hepatocellular damage[22].

In our study, PBMC of cirrhotic patients expressed more TLR2 and TLR4 under NE conditions than PBMC of non-cirrhotic patients. Exposure to LPS and LTA decreased expression of both receptors in all patients. (Figure 1B and C) A similar decrease in TLR2 expression was observed by Riordan et al. after exposing PBMC of cirrhotic patients to gram-positive bacteria products *in vitro*. However, *in vivo*, they observed an increased PBMC expression of TLR2, but not TLR4, in cirrhotic subjects[4]. It has been shown recently, that monocyte expression of TLR4 is down-regulated in cirrhotic patients with Child-Pugh class C, whereas TLR2 expression is equivalent to controls. In our study, we included patients with Child-Pugh class A or B mainly, or patients with a reasonably preserved liver function and immune competence. TLR4 down-regulation in advanced cirrhosis is associated with

LPS tolerance, enhanced bacterial translocation and portal venous endotoxemia[23]. In this context, endotoxin tolerance is viewed as a regulation mechanism that protects the cell from "over expression" or sustained activation. It is regarded as a protection mechanism that aims to limit tissue damage due to excessive immune response. Another explanatory mechanism of TLR down-regulation is receptor internalization, which has been shown for TLR2 and TLR4[24].

After exposure to LPS, PBMC of both cirrhotic and non-cirrhotic patients showed a lower TLR2 and TLR4 expression. A similar but smaller decrease was observed after LTA exposure, suggesting that these two TLRs might not be completely specific. It is well documented that TLR2 recognizes LPS as well as LTA, while TLR4 recognizes LPS mainly [5,25]. From our results, we can not exclude a cross-recognition of LPS and LTA that could lead to an "additive activation" of signaling pathways.

Differences and changes in CD14, TLR2 and TLR4 expression observed in our study support the so called hyperactivation state in cirrhotic patients which, compared to the non-cirrhotic patients, does not appear to be an uncontrolled response, but a process of cellular reprogramming or adaptation to bacteria or their products[26]. We should point out that our non-cirrhotic controls had dyslipidemia, peptic ulcer disease, hypothyroidism, major depression, diabetes, hypertension, and/or achalasia. It is known that some of these entities compromise, up to certain degree, the immune response. In spite of this, PBMC response to bacterial stimuli among cirrhotic patients was significantly different to their non-cirrhotic counterpart.

### *TNFα, IL-1β, IL-6, IL-12 and IL-10 secretion*

Cytokines, chemokines, and growth factors such as TNFα, IL-1β, IL-6, interferon-γ, IL-8, macrophage inflammatory protein-1, macrophage chemoattractant factor-1, and transforming growth factor, are all upregulated in patients with cirrhosis[1]. This upregulation varies according to the degree of liver damage, or Child-Pugh score[4, 19]. *In vitro*, PBMC exposure to bacterial and viral ligands results in an elevated production of inflammatory cytokines, particularly IL-1β, IL-6, IL-8, and TNFα,β[16]. In our study, PBMC exposure to LPS or LTA triggered a significant TNFα, IL-1β, IL-6, IL-12 and IL-10 secretion in both cirrhotic and non-cirrhotic patients. Due to sample size restrictions, no correlation with the Child-Pugh score was observed.

LPS elicited a more vigorous cytokine secretion than LTA, irrespective of the presence or absence of cirrhosis. This "attenuated" response to LTA has been observed by other investigators and attributed, *in vivo*, to serum components such as lipoproteins and LBP[19,27]. *In vitro*, to get a proinflammatory response in monocytes and hepatic stellate cells, the minimal active concentration of PGN or LTA needs to be 100 times higher than that of LPS[1]. We used 0.1 μg/mL of LTA and LPS based on dose-response experiments. With this exposure dosage, the highest TNFα secretion was obtained, which was quantitatively lower for LTA than LPS.

As to IL-6, a higher secretion was observed after LTA than after LPS exposure. This cytokine plays a pivotal role in the acute response to bacterial products. Wang et al. reported that whole human blood is a potent source of IL-6 production after stimulation with *S. aureus* LTA[28]. However, other investigators failed to induce IL-6 release from monocyte cultures[29]. This discrepant IL-6 secretion has been attributed to non-monocytic cells present in the whole blood, not well characterized paracrine factors absent in monocyte cultures[28], variable LTA exposure dosage[20], and inter- and intra-species LTA variations[29].

We should consider that, in cirrhosis, the innate immunity hyper-responsiveness observed in this and other studies do not occur in isolation to alterations in adaptive immunity. It is known that cirrhotic patients are prone to get frequent bacterial infections due to an immunosuppressed state. Contrary to the expected, their T lymphocytes are activated. The proportion of CD4+ T cells expressing CD25 and CD122 antigens is increased significantly, and so is the proportion of memory CD4+ and CD8+ T cells with characteristics of senescent cells. It is thought that repeated cycles of inflammation and damage lead to a continuous recruitment of effector leucocytes within the liver and amplify effector responses exerted by T cells, macrophages, natural killer cells or neutrophils[30]. The contribution of these immune derangements, separately and as a whole, to chronic liver injury remains to be documented.

PBMC of cirrhotic patients show a hyperactivation state in terms of CD14, TLR2 and TLR4 expression. Exposure to LPS or LTA decreases this expression in both cirrhotic and non-cirrhotic PBMC, suggesting that control mechanisms are still present in chronic liver disease. Given that PBMC receptor expression changed after exposure to both LPS and LTA, our data suggest a non-specific cross-activation. Decreased CD14, TLR2 and TLR4 expression is accompanied by an increased TNFα, IL-1β, IL-6, IL-12 and IL-10 secretion. This secretion is relatively higher in cirrhotic than non-cirrhotic patients. How this systemic hyperactivation relates to the progression of liver injury is still speculative. Both LPS and LTA elicit a PBMC response, but to a different degree. The impact of this differential response needs to be evaluated, particularly when potentially beneficial gram-positive bacteria (probiotics) are involved.

## COMMENTS

### *Background*

Liver diseases figure as the fifth cause of death in Mexico. They are the third cause of death in subjects between 35-44 years, and the fourth cause of death in subjects aged 45-64 years. Patients with advanced chronic liver disease or cirrhosis frequently present with intestinal bacterial overgrowth of both gram-negative and gram-positive bacteria. This leads to infectious complications such as spontaneous bacterial peritonitis or sepsis, and to a chronic proinflammatory state.

### *Research frontiers*

The role of gram-negative bacteria in the pathogenesis of liver injury has been extensively studied. It involves intestinal bacterial translocation and decreased

liver clearance, leading to inflammation, tissue injury and, eventually, cirrhosis. As to gram-positive bacteria, a similar damaging role has been proposed, but still remains to be proven.

### Innovations and breakthroughs

It became clear that lipopolysaccharide, a gram-negative bacterial cell wall product, cannot reproduce all the clinical features observed in sepsis. This emphasizes the participation of other contributing factors. Gram-positive bacteria, which lack lipopolysaccharide, are responsible today for a substantial part of sepsis incidence. Peripheral blood mononuclear cells of cirrhotic patients are able to respond to a sudden bacterial ligand exposure, particularly lipopolysaccharide, in terms of a decreased expression of CD14, Toll-like receptor 2 and 4, and an increased tumor necrosis factor $\alpha$, interleukin (IL)-1$\beta$, IL-6, IL-12 and IL-10 secretion. The authors suggest that immune regulation mechanisms persist in chronic liver disease, at least in Child-Pugh A and B stages.

### Applications

Both lipopolysaccharide and lipoteichoic acid elicit a peripheral blood mononuclear cells response, but to a different degree, suggesting that gram-positive microbial stimuli might be important in the proinflammatory state of chronic liver disease. The impact of this differential response needs to be evaluated, particularly when potentially beneficial gram-positive bacteria (probiotics) are involved. Current evidence shows that probiotic use is associated with a significant increase of fecal lactobacilli and a decrease of potentially pathogenic gram-positive and gram-negative bacterial species.

### Terminology

Intestinal bacterial overgrowth is a major promoting factor of bacterial translocation in cirrhosis. It is defined as bacterial migration from the intestinal lumen to the mesenteric lymph nodes or other extra-intestinal sites. Sepsis is a common cause of death in cirrhotic patients. Toll-like receptors are transmembrane receptor proteins that play a critical role in the induction of innate immunity to microbial pathogens *via* recognition of conserved molecular patterns.

### Peer review

The paper is very scientific, has copious data and is well written.

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En este artículo se trabajo con células mononucleares obtenidas de sangre periférica de pacientes cirróticos y de voluntarios sanos. De manera interesante encontramos que la respuesta de estas células a la exposición de ligandos bacterianos fue muy similar lo cual nos llevó a concluir que los mecanismos de regulación inmunológica de céulas periféricas de pacientes con cirrosis aun están presentes. Un dato importante y consistente con los resultados del trabajo doctoral es la situación basal de “sobre-estimulación” de las células de los pacientes con cirrosis probablemente en relación con una traslocación persistente.

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BRIEF ARTICLE

# PPIs are not associated with a lower incidence of portal-hypertension-related bleeding in cirrhosis

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## Abstract

**AIM:** To determine if proton pump inhibitor use in cirrhotic patients with endoscopic findings of portal hypertension is associated with a lower frequency of gastrointestinal bleeding.

**METHODS:** Patients with cirrhosis and endoscopic findings related to portal hypertension, receiving or not receiving proton pump inhibitor (PPI) therapy, were included retrospectively. We assigned patients to two groups: group 1 patients underwent PPI therapy and group 2 patients did not undergo PPI therapy.

**RESULTS:** One hundred and five patients with a median age of 58 (26-87) years were included, 57 (54.3%) of which were women. Esophageal varices were found in 82 (78%) patients, portal hypertensive gastropathy in 72 (68.6%) patients, and gastric varices in 15 (14.3%) patients. PPI therapy was used in 45.5% of patients ($n$ = 48). Seventeen (16.1%) patients presented with upper gastrointestinal bleeding; in 14/17 (82.3%) patients, bleeding was secondary to esophageal varices, and in 3/17 patients bleeding was attributed to portal hypertensive gastropathy. Bleeding related to portal hypertension according to PPI therapy occurred in 18.7% ($n$ = 9) of group 1 and in 14% ($n$ = 8) of group 2 (odds ratio: 0.83, 95% confidence interval: 0.5-1.3, $P$ = 0.51).

**CONCLUSION:** Portal hypertension bleeding is not associated with PPI use. These findings do not support the prescription of PPIs in patients with chronic liver disease with no currently accepted indication.



**Key words:** Drug prescription; Liver cirrhosis; Portal hypertension; Proton pump inhibitors; Upper gastrointestinal bleeding

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## INTRODUCTION

Since their first clinical use, proton pump inhibitors (PPIs)

have provided benefits in the management of gastrointestinal diseases. This class of drugs is clearly indicated for the treatment of peptic ulcer disease, gastroesophageal reflux disease (GERD), and nonvariceal upper gastrointestinal bleeding, and for prophylaxis in selected users of nonsteroidal anti-inflammatory drugs (NSAIDs)[1,2]. Unfortunately, the unnecessary prescription of PPIs has become an important problem, which increases economic costs in daily clinical practice[3,4]. According to previous studies in the clinical context, only 12.3% of cirrhotic patients have an appropriate indication for the prescription of these drugs[5]. Congestive gastropathy and esophageal and gastric varices are risk factors for the inappropriate use of PPIs[5].

Few studies, other than pharmacological studies, have investigated the safety and utility of PPIs in cirrhotic populations[6-9]. There are reports of possible hepatotoxicity associated with the use of PPIs in patients with chronic liver disease (CLD)[9], but there have been no clinical or experimental trials on the adverse effects of PPIs in the treatment of acute or chronic complications in patients with cirrhosis and portal hypertension (PH). Some data on the possible use of PPIs for the long-term prophylaxis of variceal bleeding exist[10], and a recent controlled trial by Zhoe *et al*[11] compared the efficacy of octreotide, vasopressin, and omeprazole for controlling acute bleeding associated with portal hypertension gastropathy. However, more clinical evidence is required. The use of this class of drugs in cirrhotic patients seems more habit-related than evidence-based, ultimately leading to an increase in health costs.

In patients with cirrhosis and PH, upper gastrointestinal bleeding has an annual frequency of 25%-35%, and 80%-90% is of variceal origin. The mortality related to variceal bleeding is about 30% per episode, and is recurrent in 70% of patients after the first year[12-15].

Considering the current paradigm of evidence-based medicine, the use of PPIs in patients with cirrhosis and endoscopic findings of PH is based only on expert opinion, with insufficient evidence to justify the use of these drugs as prophylaxis for variceal bleeding. The aim of this study was to determine whether the use of PPIs in patients with cirrhosis and endoscopic findings of PH (esophageal or gastric varices, or portal hypertensive gastropathy) is associated with a reduction in the frequency of gastrointestinal bleeding secondary to PH.

## MATERIALS AND METHODS

We conducted a retrospective, observational, longitudinal, comparative study of outpatients with CLD and endoscopic evidence of PH, receiving or not receiving treatment with PPIs, between December 1, 2004 and January 1, 2006. The endoscopic data considered for PH were esophageal varices, gastric varices, and portal hypertensive gastropathy. The sample comprised a series of consecutive patients with clinical, biochemical, endoscopic, radiological, and/or histological signs of cirrhosis and PH who attended our gastroenterology and liver clinic. We included all patients over 18 years of age who had been reviewed on at least two visits over the course of one year during the period of the study. All patients with incomplete electronic or paper charts, with no confirmatory endoscopic study at the time of the bleeding episode, were excluded from the study. These patients formed a subset of patients included in our previous work[5]. Reasons for exclusion from the present study were absence of endoscopic evidence of PH ($n$ = 80), and no previous endoscopy ($n$ = 28).

The primary demographic and medical variables were age, sex, etiology of CLD, diagnosis of hepatocellular carcinoma, liver function tests, presence of ascites, encephalopathy, the model end-stage liver disease (MELD) score, and previous use of NSAIDs (at least five times per week during the last six months), cyclooxygenase-2 inhibitors, corticosteroids, anticoagulants, and aspirin. Any hospital stay associated with portal hypertensive bleeding was also recorded.

An endoscopic procedure was performed in all patients as an initial approach. Any patient with first endoscopy at the time of an episode of active bleeding was included. The primary endpoint of our study was the presence of portal hypertensive bleeding. We defined bleeding related to PH as any bleeding episode secondary to the rupture or erosion of esophageal or gastric varices and/or portal hypertensive gastropathy, manifested clinically as melena or hematemesis. All patients with suspected variceal bleeding during the period of the study were required to have an endoscopic procedure in the first 24 h after presentation. A regular diagnostic endoscope was initially used (GIF-100, GIF-130, GIF-140, or GIF-160; Olympus, Japan). The presence of esophageal or gastric varices, portal hypertensive gastropathy, red signs, and the size of the varices were recorded according to the Baveno Ⅳ consensus[16]. Other variables assessed included nonliver-related findings such as esophagitis, hiatal hernia, erosive gastritis, and duodenal or gastric ulcer.

The use of PPIs and other medical prescriptions within the six months preceding the study were identified in the patients' records. We defined PPI users as those patients with cirrhosis who had taken 20 mg of omeprazole (or an equivalent dose of any other PPI) for at least eight weeks before the episode of portal hypertensive bleeding or initial evaluation (first considered visit). Confirmation of the patients' compliance with the PPI treatment was based on chart records. A diagnosis of GERD was made according to the definition: "a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications"[17]. Troublesome symptoms were defined by the patient as affecting his/her quality of life. The symptoms considered were heartburn, regurgitation, reflux-related chest pain, extraesophageal syndromes of GERD (laryngitis, cough, asthma) confirmed by their resolution with PPI therapy, pH monitoring, or endoscopic evidence of esophagitis, according to the Los Angeles classification (grades B, C, or D)[17].

### *Statistical analysis*

The results are expressed as distributions, absolute frequencies, relative frequencies, medians and ranges, or

means ± SD. For comparison, patients were classified into two groups: patients who used PPIs and patients who did not use PPIs. The quantitative data were compared using the Student's *t*-test for variables with a normal distribution, and the Mann-Whitney *U* test for other variables. Differences between the proportions of categorical data were evaluated with Fisher's exact test when the number of expected subjects was less than five and otherwise with the $\chi^2$ test. A multivariate logistic regression model was used to assess the independent association between PPI use and bleeding related to PH. A *P* value of $< 0.05$ was considered statistically significant.

### Sample size calculation

According to data published by Hajime *et al*[10] the frequencies of variceal bleeding in patients with and without PPI use were 10% and 52.4%, respectively (a difference of 42%). According to these data, to detect a difference of at least 42%, we required at least 25 patients for each group (group 1, patients with cirrhosis and PPI use; and group 2, patients with cirrhosis and no PPI use). All statistical analyses were conducted with SPSS statistical software (v. 12.0; SPSS Inc., Chicago, IL, USA).

## RESULTS

We initially evaluated 135 patients. Thirty patients were excluded because of incomplete data, therefore, a total of 105 patients were included in the study. The characteristics of the included patients are shown in Table 1. The most frequent endoscopic finding was esophageal varices in 82 (78%) patients, 16 (19.5%) of whom were recorded as having large varices and/or red signs. Portal hypertensive gastropathy was found in 72 patients (68.6%) and gastric varices in 15 patients (14.3%). Of those patients with gastric varices, 13/15 (86.6%) also had esophageal varices. Other findings not related to CLD were erosive gastropathy in 14 patients (13.3%), hiatal hernia in eight patients (7.6%), duodenal ulcer (Forrest Ⅲ) in three patients (2.9%), and gastric ulcer (Forrest Ⅲ) in three patients (2.9%). Other comorbidities are shown in Table 1. There was a tendency [odds ratio (OR): 1.3, 95% confidence interval (CI): 0.72-2.6, $P = 0.2$] to non-portal hypertension-related bleeding episodes ($n = 20$; erosive gastropathy, duodenal ulcer, and gastric ulcer) in patients not using PPIs.

Forty-eight (45.5%) patients underwent PPI therapy. Most of these patients used omeprazole, although 10 used pantoprazole. During the period of evaluation, 16.1% ($n = 17$) presented with upper gastrointestinal bleeding related to PH, and in 82.3% of these patients ($n = 14$), this bleeding was secondary to esophageal varices, whereas in three patients it was attributable to portal hypertensive gastropathy. We recorded no episodes of bleeding secondary to gastric varices. When we analyzed the presence of variceal bleeding in patients classified according to their pattern of PPI use (group 1, patients using PPI, $n = 48$; and group 2, patients not using PPI, $n = 57$), the frequency was 18.7% ($n = 9$) in group 1 and 14% ($n = 8$) in group 2 (OR: 0.83, 95% CI: 0.5-1.3, $P = 0.51$). When we evaluated only those patients with upper gastrointestinal bleeding secondary to esophageal varices, we observed frequencies of 12.5% in group 1 and 14% in group 2 (OR: 1.07, 95% CI: 0.56-2.0, $P = 0.81$). A comparison of the characteristics of patients using PPIs and those not using PPIs is shown in Table 1.

**Table 1 Characteristics of the patients included in the study classified by proton pump inhibitor use (mean ± SD) *n* (%)**

| Variable | Patients using PPIs ($n = 48$) | Patients not using PPIs ($n = 57$) | *P* value |
|---|---|---|---|
| Age (yr) | 56.1 ± 13.8 | 57 ± 12.4 | 0.71 |
| MELD | 12.8 ± 6.3 | 11.5 ± 5.4 | 0.25 |
| CPT | 8.3 ± 1.8 | 7.2 ± 2.2 | 0.55 |
| Albumin (g/L) | 28 ± 0.6 | 32 ± 1.5 | 0.16 |
| Total bilirubin (mg/L) | 27 ± 3.7 | 24 ± 3.3 | 0.62 |
| ALT (UI/L) | 47.2 ± 22.6 | 50 ± 40.5 | 0.66 |
| Alkaline phosphatase (UI/L) | 161.2 ± 92.2 | 132.9 ± 63.8 | 0.06 |
| BMI | 26.5 ± 4.4 | 25.9 ± 3.7 | 0.46 |
| Sex, male | 19 (40) | 29 (51) | 0.24 |
| Etiology | | | |
| Viral hepatitis C | 25 (52) | 25 (44) | 0.44 |
| Alcohol | 12 (25) | 12 (21) | 0.56 |
| Cryptogenic | 5 (10) | 10 (18) | 0.28 |
| Autoimmune hepatitis | 2 (4) | 8 (14) | 0.22 |
| Other | 4 (8) | 2 (4) | 0.26 |
| Child-pugh-turcotte | | | |
| A | 19 (40) | 31 (54) | 0.2 |
| B | 22 (46) | 17 (30) | 0.3 |
| C | 7 (15) | 9 (16) | 0.4 |
| GERD | 7 (15) | 5 (9) | 0.7 |
| Gastric/esophageal varices | 44 (92) | 40 (70) | 0.006 |
| Large | 6 (13) | 3 (5) | 0.1 |
| Red signs | 4 (8) | 3 (5) | 0.35 |
| Responders to β-adrenergic blocker | 13 (27) | 11 (19) | 0.34 |
| NSAID | 4 (8) | 0 (0) | 0.04 |
| Antiplatelet agents use | 7 (15) | 5 (9) | 0.1 |
| Oral anticoagulation | 1 (2) | 1 (2) | 0.9 |
| Steroid use | 3 (7) | 2 (4) | 0.37 |
| Comorbidities | | | |
| Diabetes mellitus | 19 (40) | 28 (49) | 0.43 |
| Hypertension | 9 (19) | 14 (25) | 0.63 |
| High-level triglycerides | 3 (6) | 10 (18) | 0.13 |

CPT: Child-pugh-turcotte class; GERD: Gastroesophageal reflux disease; MELD: Model for end stage liver disease; PPIs: Proton pump inhibitors; ALT: Alanine aminotransferase; NSAID: Non-Steroidal anti-inflammatory drugs; BMI: Body mass index (calculated as patient body weight divided by the square of their height expressed in kg/m$^2$).

The overall prevalence of GERD was 11.4% ($n = 12$), corresponding to 14.5% of group 1 ($n = 7/48$). Only seven (57.1%) patients with GERD received PPIs. Of the total number of patients with portal hypertensive bleeding, 11.7% ($n = 2/17$) had GERD. The presence of GERD was not statistically significantly associated with the presence of upper gastrointestinal bleeding (OR: 0.53, 95% CI: 0.15-1.8, $P = 0.31$). Univariate and multivariate analyses of the variables associated with gastrointestinal bleeding secondary to PH are shown in Table 2.

## DISCUSSION

In this study, we observed that in patients with CLD and endoscopic evidence of PH, the presence of gastrointes-

**Table 2 Univariate and multivariate analyses of risk factors associated with portal-hypertension related bleeding in cirrhotic patients**

| | B Coefficient | Standard error | Wald $\chi^2$ | OR (95% CI) | *P* value |
|---|---|---|---|---|---|
| Univariate | | | | | |
| Age ⩾ 60 | - | - | - | 1.1 (0.37-3.5) | 1 |
| Sex, male | - | - | - | 1.7 (0.5-5.2) | 0.39 |
| CPT C | - | - | - | 1.6 (0.40-6.6) | 0.36 |
| GERD | - | - | - | 0.53 (0.15-1.8) | 0.31 |
| MELD > 15 | - | - | - | 1.2 (0.35-4.4) | 0.47 |
| PPI use | - | - | - | 0.83 (0.5-1.3) | 0.51 |
| LEV | - | - | - | 12 (3-123) | < 0.001 |
| Red signs | - | - | - | 10 (2-58) | < 0.001 |
| NSAID | - | - | - | 0.86 | 0.55 |
| Multivariate | | | | | |
| LEV | 23.7 | 15.1 | 0 | 10 (4-110) | < 0.001 |
| Red signs | 22.0 | 14.2 | 0 | 9 (4-102) | < 0.001 |

CPT C: Child-pugh-turcotte class C; GERD: Gastroesophageal reflux disease; MELD: Model for end stage liver disease; PPI: Proton pump inhibitor; LEV: Large Esophageal varices; NSAID: Non-steroidal anti-inflammatory drugs; OR: Odds ratio; CI: Confidence interval.

tinal bleeding secondary to variceal or portal hypertensive gastropathy was not associated with the use of PPIs. This is a very important finding because it has been reported that the presence of PH on endoscopy is associated with an unacceptable, and according to our data, unnecessary prescription of PPIs in patients with cirrhosis[5,18].

Soon after the introduction of PPIs into clinical practice, these drugs demonstrated their effectiveness in several gastrointestinal diseases. However, the overuse of this class of drugs has important economic implications. In patients with cirrhosis, many factors influence the appropriate prescription of PPIs[5,18]. It was observed in previous studies that patients in the early stages of Child-Pugh-Turcotte classification, and with a low MELD score, were more likely to be prescribed PPIs appropriately than those in the more advanced stages of the disease or with endoscopic findings of PH[5,18]. According to the scarce evidence available regarding the use of these drugs in the clinical context, it seems that physicians tend to consider the use of PPIs in cirrhotic patients as possibly beneficial for variceal bleeding. It has also been postulated in the past that gastroesophageal reflux may contribute to esophagitis and variceal bleeding in patients with CLD[19]. In fact, there are few data on the use of PPIs in these patients, and these data are predominantly related to the pharmacological properties of the drugs[20]. The findings of our study are consistent with those of other studies, which have reported that patients with PH, and especially those with portal hypertensive gastropathy, display increased bicarbonate production and an elevated gastric pH. The increased circulatory rate in these patients, the high gastric pH level, and the increased prevalence of hypochlorhydria are factors associated with lower pepsin activity[21-25].

The main limitation of our study is its retrospective design. However, data concerning the association of portal hypertensive bleeding with the use of PPIs are scarce and are based on only one study, published as an abstract[10]. There is an absence of data from randomized trials, thus, prospective studies are still required to develop more reliable recommendations regarding the use of PPIs in this context. The diagnosis of PH in this study was based on esophageal varices, gastric varices, and hypertensive gastropathy, therefore, it is possible that some patients with a hepatic venous pressure gradient above 12 mmHg were overlooked. However, our study focused on patients with endoscopic findings related to PH.

In conclusion, our data support the hypothesis that the use of PPIs is not associated with upper gastrointestinal bleeding related to PH in cirrhotic patients. Therefore, these findings do not support the use of PPIs in patients with CLD and endoscopic evidence of PH without a currently accepted indication.

## COMMENTS

### *Background*

Gastrointestinal bleeding secondary to portal hypertension is a major complication in patients with cirrhosis, and proton pump inhibitors are frequently used to prevent it. These drugs have provided benefits in the management of many gastrointestinal disorders; unfortunately, the unnecessary prescription of these drugs has become an important problem, which increases costs in daily practice. Considering the current paradigm of evidence-based medicine, their use in patients with cirrhosis and portal hypertension is based only on expert opinion, with insufficient evidence to justify the use of these drugs as prophylaxes.

### *Research frontiers*

Proton pump inhibitors are widely used among patients with chronic liver disease and endoscopic findings of portal hypertension with the aim of preventing bleeding, however, there is no appropriate evidence to support their use for this condition. In this study, the authors demonstrate that the use of proton pump inhibitors is not associated with a lower frequency of gastrointestinal bleeding in cirrhotic patients.

### *Innovations and breakthroughs*

In this study, the authors observed that in patients with chronic liver disease and endoscopic evidence of portal hypertension, the presence of gastrointestinal bleeding secondary to variceal or portal hypertensive gastropathy was not associated with the use of proton pump inhibitors. This is a very important finding because it has been reported that the presence of portal hypertension on endoscopy is associated with an unacceptable, and according to the data, unnecessary prescription of proton pump inhibitors in patients with cirrhosis.

### *Applications*

This study provided evidence on the use of proton pump inhibitors in patients with chronic liver disease and endoscopic findings of portal hypertension, and does not support their use without a currently accepted indication for their prescription in this group of patients.

### *Terminology*

Proton pump inhibitors are a class of drugs that reduce the secretion of HCl in the stomach, consequently increasing gastric pH. The current principal accepted indications for these drugs include peptic ulcer disease and gastroesophageal reflux disease. Esophageal varices and hypertensive gastropathy are referred to as endoscopic findings of portal hypertension. Portal hypertension is the main cause of gastrointestinal bleeding in patients with cirrhosis, and its prevention is very important in clinical practice.

### *Peer review*

This is a clear cut-off of the question of non-steroidal anti-inflammatory drugs with/without proton-pump inhibitors administration dilemma. The clinical problem is well addressed and presented, and the authors provide a rationale for their conclusions.

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**S- Editor** Sun H **L- Editor** Webster JR **E- Editor** Ma WH

Este artículo es particularmente interesante y se encuentra en línea directa con otro trabajo previo publicado por nuestro grupo que no incluimos en la lista para reconocimiento de publicaciones (Med Sci Monit. 2008;14(9):CR468-72.). Ambos están dirigidos a explorar la prevalencia y factores asociados al uso de inhibidores de bomba de protones (IBP) de manera inapropiada en pacientes con cirrosis. Ambos artículos documentaron que el uso de IBP en los pacientes cirróticos se lleva a cabo sin una indicación clara y que pareciera asociarse a la gravedad de los pacientes. Estos artículos han originado otras investigaciones de otros grupos (comunicación verbal con los autores de dichos trabajos): Aliment Pharmacol Ther. 2012 Sep 11. doi: 10.1111/apt.12045. [Epub ahead of print]

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# Bacterial Meningitis in Cirrhotic Patients

## *Case Series and Description of the Prognostic Role of Acute Renal Failure*

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**Aim:** To analyze the mortality risk factors in cirrhotic patients with bacterial meningitis (BM).

**Background:** Cirrhotic patients are susceptible to infections. Despite its high mortality rate, BM has not been extensively studied in this group of patients.

**Study:** BM patients diagnosed with cirrhosis, between 1987 and 2008, were studied. BM was defined as the presence of signs or symptoms of meningitis and a cerebrospinal fluid (CSF) leukocyte count $> 100/mm^3$ or the presence of bacteria in CSF.

**Results:** We identified 4955 infections among 7591 cirrhotic patients; 12 (0.2%) had BM. The mean age at diagnosis was $60 \pm 16$ years. Abnormal mental status (83%), fever (67%), and neck stiffness (67%) were the most frequent clinical presentations. The sensitivity of CSF culture was 75% (*Streptococcus pneumoniae*, 2; *Staphylococcus aureus*, 2; *Listeria monocytogenes*, 1; Group B Streptococcus, 1; *Streptococcus agalactiae*, 1; *Streptococcus bovis*, 1; and *Escherichia coli*, 1), and its correlation with blood culture was 78%. Five patients died. On admission, the serum creatinine level was $1.63 \pm 0.93$ mg/dL. A serum creatinine level $\geq 1.3$ mg/dL was associated with increased mortality ($P = 0.028$). The model for end-stage liver disease score, gastrointestinal bleeding, bilirubin level $> 3.5$ mg/dL, hepatic encephalopathy, diabetes mellitus, and results of cytology and biochemistry tests of CSF were not associated with mortality.

**Conclusions:** BM in cirrhotic patients is associated with a high mortality rate. The clinical and microbiologic features of BM in cirrhotic patients differ from those in the general population. A serum creatinine level $\geq 1.3$ mg/dL on admission is associated with a higher risk of mortality.

**Key Words:** meningitis, liver cirrhosis, prognosis, infection, central nervous system diseases, acute renal failure, Mexico, Guatemala

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Bacterial infections represent 30% to 50% of hospital admissions, and are responsible for one-third of the deaths in patients with chronic liver disease (CLD). The most common bacterial infections are spontaneous bacteremia, pneumonia, and urinary infection. Among patients with ascites, the most common infection is spontaneous bacterial peritonitis (SBP), followed by bacteriascites.[1–5] Although in a few case series a high proportion of patients with meningitis caused by pneumococci or Gram-negative bacilli also had liver cirrhosis or liver disease, the risk and prognosis of bacterial meningitis (BM) in patients with CLD are unknown.

The increased susceptibility for infections in cirrhotic patients is because of an altered immunologic system, malnutrition, and alcohol intake.[6] Perney et al[7] showed that alcoholic patients have altered immunity because of the function of natural killer cells and diminished expression of perforin. Moreover, the activity of peripheral mononuclear cells induced by interleukin-2 and the production of interferons are diminished.[8] Other mechanisms, such as, reduced activities of polymorphonuclear cells and free radicals, phagocytosis, chemotaxis, and an altered response to bacterial stimuli are observed.[9,10]

The incidence of community-acquired BM in the general population is 5 per 100,000 adults per year; 80% of these are caused by *Streptococcus pneumoniae* and *Neisseria meningitides*.[11] Central nervous system infections in patients with CLD have been described[12–17]; they have a 10-fold increased risk than that reported for the general population (54.4/100,000 per year).[15] Approximately 4.8% of the patients with community-acquired BM are cirrhotic[13], and the mortality rate is reported to increase from 52% to 63% ,and even higher in older patients and those with alcohol-induced cirrhosis.[15,16] Reported risk factors for BM in cirrhotic patients include endoscopic procedures[17–19] and infections elsewhere,[20] in cirrhotic patients with BM, besides the usual agents, *Listeria monocytogenes* and *Cryptococcus neoformans* should also be considered.[18,21–24] Inspite of this discussion there is not enough evidence to support the risk factors used to predict mortality presenting any infection are those reported in SBP.

In clinical practice, estimation of serum creatinine is still the most useful and widely accepted method for the assessment of renal function in patients with cirrhosis.[25,26] In cirrhotic patients, several underlying conditions contribute to a false decreasing in serum creatinine concentration, even in the presence of a moderate-to-severe renal impairment, causing overestimation of true glomerular filtration

rate.[27] Therefore, we decided to decrease the cut-off value from 1.5 mg/dL [in patients with hepatorenal syndrome (HRS)][26,28,29] to 1.3 mg/dL (in patients without HRS). The aim of this study is to describe the clinical and biochemical features of a case series of patients with BM and CLD, and describe the risk factors associated with mortality, emphasizing on renal function.

## METHODS

We analyzed electronic files and paper records of the patients diagnosed with cirrhosis between 1987 and 2008. Patients who had been discharged at least once with a diagnosis of BM were included in the study. The diagnosis of cirrhosis was established using clinical characteristics, laboratory tests, ultrasonography, and/or histologic analysis.

Bacterial meningitis was defined as the presence of its bacterial in CSF culture and/or elevated leukocyte count ($>100$ cells/mm$^3$), with more than 90% of polymorphonuclear leukocytes in the CSF of a patient with signs or symptoms suggesting the infection.[13] The purpose of this procedure was to avoid dubious cases and strengthen the validity of the diagnoses.

Acute renal failure was defined as elevation of twice the basal measure of creatinine or, when there was no previous information, $\geq 1.3$ mg/dL. We analyzed the serum creatinine levels in the outpatient evaluation before admission (basal creatinine level) and compared those with the values obtained on admission. Creatinine values during hospitalization and follow-up were not analyzed because it is known that during this period the level of serum creatinine is influenced by several factors, which are not in the scope of this study.

The severity of hepatic failure was assessed according to the Child-Pugh-Turcotte score and the model for end-stage liver disease (MELD). Hyponatremia was defined as a serum sodium concentration $\leq 135$ mmol/L and hypernatremia as a serum sodium concentration $\geq 145$ mmol/L. Variceal bleeding was caused by the rupture or erosion of esophageal or gastric varices in cirrhotic patients with portal hypertension, clinically presented as hematemesis, melena, melanemesis, and/or hematochezia; patients with upper gastrointestinal bleeding because of hypertensive gastropathy were considered as equivalent. In all cases, upper endoscopy was performed to assure or discard the diagnosis. Mortality was assessed in a 90-day period after the diagnosis of BM. Every patient received antibiotic therapy, which was prescribed by an expert in infectious diseases.

### Statistical Analysis

Data are expressed in absolute frequencies, relative frequencies, medians, and minimum-maximum intervals. Numerical variables were analyzed by the Mann-Whitney *U* test and categorical variables by the Fisher exact probability test. Odds ratio associated with mortality was obtained. Statistical significance was considered with a $P$ value $\leq 0.05$. Statistical analysis was conducted using the statistics program SPSS/PC v. 13.0 (SPSS, Chicago, IL).

## RESULTS

Among a cohort of 7591 patients with CLD, we identified 2710 patients with 4955 infectious episodes (mean: 1.8 episodes/patient). Twelve cirrhotic patients fulfilled the diagnostic criteria of BM, representing 0.2% of the total amount of infectious episodes (4.4 cases/1000 patients). Eight patients (67%) were women and 4 (33%) were men. The median age at diagnosis of BM was 63 (range: 31-86) years. Etiology of cirrhosis was alcohol abuse in 7 patients (58%), hepatitis C viral infection in 4 patients (33%), and cryptogenic in 1 patient (8%). Seven patients (58%) were diagnosed with type 2 diabetes mellitus.

Clinical presentation of BM was abnormal mental status in 10 patients (83%, including 3 patients in coma), fever in 8 patients (67%), neck stiffness in 8 patients (67%), headache in 6 patients (50%), irritability in 6 patients (50%), vomiting in 4 patients (33%), convulsive status in 3 patients (25%), Kerning sign in 6 patients (50%), Brudzinski sign in 5 patients (42%), and Babinski sign in 2 patients (17%). All the patients had at least one sign of meningeal irritation. The median time before proceeding to the emergency room was 4 (range: 1-21) days.

Nine patients (75%) had a positive CSF culture. The most commonly isolated germs were *S. pneumoniae* in 4 cases (33%) and *Staphylococcus aureus* in 2 cases (17%) (Table 1). Blood and CSF cultures correlated in 7 cases (58%). The median leukocyte count in CSF was 535 cells/mm$^3$ (range: 30-4940), and was not related with an increased risk of mortality ($P = 0.68$). Glucose concentration in CSF was 46 mg/dL (range: 0-89), and was not related with an increased risk of mortality either ($P = 0.30$).

The Child-Pugh-Turcotte score at admission was 10 (range: 6-14) and at the outcome was 11 (range: 7-15). Five patients died (42%): 4 during hospitalization (range: 2-14 days) and 1 after being discharged from the hospital (70 days). Diabetes was found in 4 of the 5 patients that died compared with 3 of the 7 patients that did not die (80% vs. 43%, $P = 0.29$). On admission, the Child-Pugh-Turcotte score, white blood cells count over the normal limit ($>10{,}000$ cells/$\mu$L), and altered serum sodium levels were not associated with an increased risk of mortality. Four patients in the group that died compared with three patients in the group that survived had ascites on admission ($P = 0.29$); none of them had peritonitis. Systolic blood pressure, on admission, was not different between the group of patients that died and the group that survived ($113 \pm 19$ vs. $115 \pm 20$ mm Hg, $P = 0.2$).

We found 7 (58%) patients with acute renal failure at admission; acute tubular necrosis was diagnosed in all of them. The median serum creatinine level at admission was 1.2 (range: 0.8-3.5) mg/dL. A 90-day mortality rate was significantly increased in patients with creatinine $\geq 1.3$ mg/dL at admission (100% vs. 28%, $P = 0.028$) (Table 2; Figs. 1 and 2). Among the patients who died, 4 out of 5 (80%) had a basal creatinine value of less than 1.3 mg/dL (range: 2-6 months before admission).

## DISCUSSION

In this study, the characteristics of a group of patients with CLD and BM have been described. High mortality (42%) rates were observed in patients with serum creatinine values $\geq 1.3$ mg/dL. According to our results, the other risk factors valid in SBP were not significant.

We identified 12 cases of BM in cirrhotic patients; although, it is a small number, our data support the fact that BM, as other infections, in cirrhotic patients is more frequent than in the general population (4.4/1000 patients vs. 5/100,000 adults per year). In this group, the etiology of cirrhosis was similar to that described earlier for the

**TABLE 1.** Etiology of Cirrhosis, Etiology of Meningitis, Complications, and Mortality of Included Patients

| | Etiology | Cerebrospinal Fluid Culture | Blood Culture | Concurrent Infection | Antibiotic Treatment | Complications | Length of Hospital Stay (d) | 90-day Mortality |
|---|---|---|---|---|---|---|---|---|
| 1 | HCV | *Staphylococcus aureus* | *S. aureus* | No | Ampicillin + Vancomycin | Hydrocephaly | 44 | No |
| 2 | Alcohol | *Listeria monocytogenes* | No | Pneumonia | Ceftriaxone | No | 17 | No |
| 3 | Alcohol | Pneumococci | Pneumococci | No | Ceftriaxone + Ampicillin + Vancomycin | Cerebral edema* | 3 | Yes |
| 4 | Alcohol | Group B streptococcus | Group B streptococcus | No | Penicillin | No | 12 | No |
| 5 | Alcohol | *S. aureus* | *S. aureus* | No | Ceftazidime + Vancomycin | SIADH* | 2 | Yes |
| 6 | Alcohol | Pneumococci | Pneumococci | Pneumonia | Ceftriaxone + Vancomycin | No | 13 | No |
| 7 | HCV | *Streptococcus agalactiae* | No | No | Ceftriaxone | No | 14 | No |
| 8 | HCV | No | Pneumococci | No | Ceftriaxone | Cerebral edema* | 12 | Yes |
| 9 | Alcohol | No | No | No | Cefepime + Amikacin + Vancomycin | Cerebral edema* | 8 | Yes |
| 10 | Alcohol | *Streptococcus bovis* | *S. bovis* | No | Ceftazidime + Ampicillin | No | 20 | No |
| 11 | Cryptogenic | No | *Pneumococci* | No | Ceftriaxone | No | 13 | No |
| 12 | HCV | *Escherichia coli* | *E. coli* | No | Ceftazidime + Ampicillin | Vegetative status, cerebral edema* | 12 | Yes |

*Cause of death.
HCV indicates hepatitis C virus; SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

Mexican population,[30–32] supporting the fact that chronic damage of the liver is a more important risk factor for BM than the etiology of cirrhosis itself. The prevalence of a positive CSF culture in our group was high (75%) as compared with the other series in which the negative CSF cultures were as high as 80%.[33] According to earlier data, the etiology of BM in cirrhotic patients differs from that of the general population; in our case series we found consistency with this information. In cirrhotic patients, *L. monocytogenes* and *C. neoformans* have been frequently reported. These microorganisms are found more often in older patients with debilitating diseases, and/or associated

**TABLE 2.** Univariate and Multivariate Analysis of Mortality and Related Risk Factors

| Variable | 90-day Follow-up Mortality, n = 5 n (%) | 90-day Follow-up Alive, n = 7 n (%) | OR (95% CI) | *P* |
|---|---|---|---|---|
| Univariate | | | | |
| Sex, female | 3 (60) | 5 (71) | 0.7 (0.2-2.8) | 0.57 |
| Age > 60 years | 3 (60) | 4 (57) | 0.9 (0.2-3.6) | 0.68 |
| Total bilirubin > 3 mg/dL | 3 (60) | 2 (29) | 0.5 (0.1-1.8) | 0.31 |
| Type 2 diabetes mellitus | 4 (80) | 3 (43) | 0.3 (0.05-2.2) | 0.24 |
| Hepatic encephalopathy | 4 (80) | 2 (29) | 0.2 (0.03-1.6) | 0.12 |
| GI bleed | 3 (60) | 5 (71) | 1.3 (0.3-5) | 0.57 |
| Creatinine ≥ 1.3 mg/dL* | 5 (100) | 2 (29) | 3.5 (1.08-11.2) | 0.02 |
| MELD ≥ 15 | 5 (100) | 4 (57) | 1.6 (0.1-24.7) | 1.00 |
| Hyponatremia ≤ 135 mmol/L | 2 (40) | 3 (43) | 1.07 (0.27-4.2) | 0.92 |
| Hypernatremia ≥ 145 mmol/L | 1 (20) | 0 (0) | 1.2 (0.8-1.9) | 0.21 |
| Albumin < 3.5 g/dL | 4 (80) | 7 (100) | 1.2 (0.8-1.9) | 0.21 |
| History of SBP | 1 (20) | 4 (57) | 1.4 (0.17-11.7) | 0.73 |
| Sepsis | 1 (20) | 2 (29) | 1.4 (0.18-11) | 0.73 |
| INR ≥ 1.5 | 4 (80) | 6 (86) | 1.07 (0.62-1.8) | 0.79 |
| Multivariate | | | | |
| Constant | — | — | 0.000 | < 0.001 |
| Creatinine ≥ 1.3 mg/dL* | — | — | 4 (1.02-10) | < 0.001 |

*Creatinine value at bacterial meningitis diagnosis.
CI indicates confidence interval; GI, gastrointestinal; INR, international normalized ratio; MELD, model for end-stage liver disease; OR, odds ratio; SBP, spontaneous bacterial peritonitis.

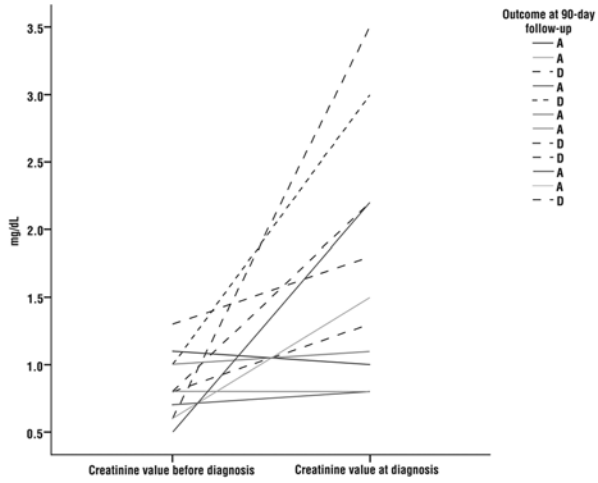


**FIGURE 1.** Basal creatinine value at admission. A indicates alive; D, death.

with an altered cellular immunity. We did not find any case of meningitis caused by *L. monocytogenes*. On the other hand, *S. aureus* has not been frequently associated with BM in cirrhotic patients, but we found 2 cases wherein 1 patient had pneumonia and the other one had suffered recent trauma.

Clinical presentation differs when compared with the general population. In our study, abnormal mental status (83%), fever (67%), and neck stiffness (67%) were the most common clinical presentations. Headache was only reported in half of our patients, suggesting that clinical presentation of BM is different in cirrhotic patients; therefore, special emphasis has to be made when performing an early diagnosis. The classic triad of BM was only present in 3 (25%) patients. In a prospective study including 696 adult patients with community acquired BM, it was reported that

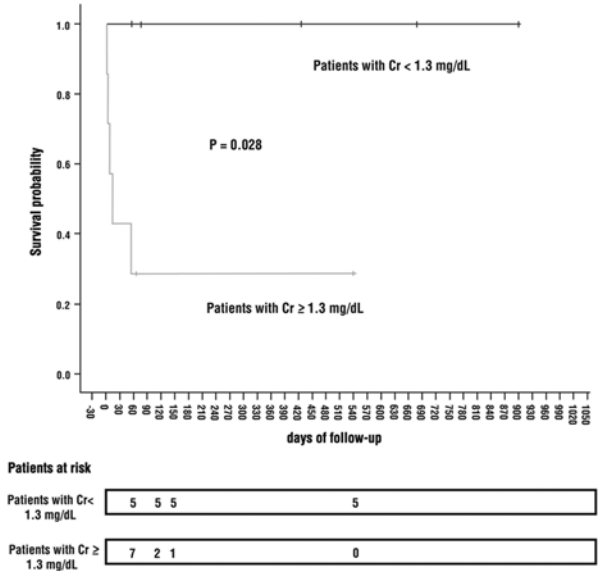


**FIGURE 2.** Comparative survival probability during the follow-up period.

headache (87%), neck stiffness (83%), and altered mental status (69%) were the most common manifestations, and the classic triad of fever, neck stiffness, and altered mental status was found in lower proportion (44%).[33] Reasons for these differences are unknown, but our results confirm the ones found by Cabellos et al.[14] It is of interest to keep in mind that abnormal mental status is the most frequent clinical presentation of meningitis, and because of this it may be mistaken for hepatic encephalopathy in patients with decompensated liver cirrhosis.

Terra et al reported that the incidence of renal failure in cirrhotic patients with sepsis was significantly higher than in patients without infection (27% vs. 8%). They also reported a higher mortality rate of 3 months in patients with nonreversible renal failure (100% vs. 60%), despite a similar rate of infection resolution (95% vs. 99%). Other studies also show that in cirrhotic patients, infections represent an increased risk of mortality.[2,3,12] In our case series, 5 of the 12 patients died. The causes of death were those associated with infection and damage to the central nervous system (Table 1). Two (16%) of our patients had pneumonia at the time of the diagnosis of BM and neither of them died. No cases of peritonitis were found, and the presence of ascites was not a risk factor for mortality. The only variable significantly associated with mortality was the serum creatinine level $\geq 1.3$ mg/dL on admission, with a sensitivity of 100% [95% confidence interval (CI), 57-100], specificity of 71% (95% CI, 36-92), positive predictive value of 71% (95% CI, 36-92), and negative predictive value of 100% (95% CI, 57-100). This is consistent with the findings in patients with SBP.[3] It has been reported that renal failure is also associated with mortality in cirrhotic patients admitted to the intensive care unit (65%, odds ratio: 4.1) when compared with patients with normal renal function (32%).[34] Neither factors related to mortality in SBP (bilirubin $> 3.5$mg/dL, hepatic encephalopathy, and upper gastrointestinal bleeding), nor the age at diagnosis of BM or the etiology of cirrhosis were associated with a higher mortality rate (Table 2). It is known that renal failure in patients with CLD is because of acute tubular necrosis in 41.7% of the cases, prerenal causes in 38%, whereas HRS represents only 20%.[35] It has been informed that in almost half of the cases of HRS, one or more precipitant factors are present: infections (57%), gastrointestinal bleeding (36%) and large volume paracentesis (7%).[36] We did not find patients achieving the diagnostic criteria for HRS; thus, our results support the idea that a severe infection can predispose to renal failure, and this represents an increased risk of mortality, as what happens in cirrhotic patients with upper gastrointestinal bleeding.[37,38] Moreover, a serum creatinine level above 1.3 mg/dL should be considered as a mortality risk factor in patients with BM; this level should be studied in other infections and in cases of acute renal failure different from HRS. Our results made us redefine the current cut-off value of serum creatinine for renal failure in patients with cirrhosis. It is important to consider that cirrhotic patients have several underlying conditions that contribute to a false decrease in serum creatinine levels, such as, decreased creatinine production secondary to a lower hepatic creatinine synthesis, reduced muscle mass, and increased tubular creatinine secretion.[27] All these factors contribute to a lower serum creatinine concentration, which often does not accurately reflect renal function; therefore, decreasing the creatinine cut-off value can help to promptly identify the high-risk patients.

To determine whether a higher cut-off value of serum creatinine is useful in identifying patients with a high risk of mortality, we analyzed the serum creatinine value $\geq 1.5$ mg/dL accepted by the International Ascites Club.[28] We observed that this value failed to discriminate the patients who had died ($P = 0.1$); although, it may be because of the small sample size.

The MELD score has been identified as an independent risk factor of mortality in cirrhotic patients with acute renal failure[39]; we observed no difference when comparing the patients who had died with those who were alive, after the 90-day follow-up period. Pathogenic mechanisms leading to renal failure could include volume depletion, shock, intrinsic renal disease (i.e., glomerulonephritis), nephrotoxicity, and sepsis. It is known that patients with CLD have increased levels of endotoxin,[40] enhanced proinflammatory cytokine response, increased production of endothelin, and activation of toll-like receptor-2, which is involved in the production of tumor necrosis factor-$\alpha$ in response to gram-positive microbial stimuli.[41] Despite advances in the knowledge of interaction between infections, renal dysfunction, and homeostasis, the complete mechanism has not been discovered.

Altered sodium level has also been identified as a risk factor in cirrhotic patients[42–45] and in patients with BM.[46] In our patients, neither hypernatremia (1 case, 8%; $P = 0.9$) nor hyponatremia (5 cases, 42%; $P = 0.23$) were associated with an increased risk of mortality. Glucose concentration and white blood cell count in CSF were not associated with an increased mortality rate.

Limitations of this study include the design and the small number of patients. Nutritional status was not estimated in an assured manner in our patients; hence, our results should be interpreted with caution. On account of a low incidence of the disease, it would be very difficult to conduct a prospective study; however, clinical and experimental studies regarding the knowledge of the complex interactions between renal and liver function in patients with infections elsewhere are warranted.

In conclusion, the incidence of BM in cirrhotic patients is higher than in the general population, and has a higher mortality rate. Clinical presentation and microbiology features are different than those reported in the general population. Serum creatinine level $\geq 1.3$ mg/dL on admission was associated with an increased risk of mortality.

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Este interesante trabajo abarcó por primera vez uno de los padecimientos infecciosos en pacientes con cirrosis fuera de la peritonitis bacteriana espontánea (PBE). Actualmente las infecciones diferentes a la PBE en pacientes cirróticos han cobrado cada vez mayor atención ya que con mayor frecuencia se reportan datos de la alta morbi-mortalidad de las infecciones en general. Sin embargo, cuando se realizó este estudio los datos acerca de meningitis en pacientes con cirrosis eran sumamente escasos. Este trabajo, creemos, aportó importante evidencia de que otros focos infecciosos en los pacientes cirróticos eran tan importante como la PBE con altas tasas de mortalidad.

**Referencias hechas a este artículo: 1**

- Bunchorntavakul C, and Chavalitdhamrong D. Bacterial infections other than spontaneous bacterial peritonitis in cirrosis. World J Hepatol 2012; 4: 158-168.

# Image-guided percutaneous procedure plus metronidazole versus metronidazole alone for uncomplicated amoebic liver abscess (Review)

**Chavez-Tapia NC, Hernandez-Calleros J, Tellez-Avila FI, Torre A, Uribe M**

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[Intervention Review]

# Image-guided percutaneous procedure plus metronidazole versus metronidazole alone for uncomplicated amoebic liver abscess

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## ABSTRACT

### Background

Metronidazole is the standard of care for uncomplicated amoebic liver abscesses (considering that complicated liver abscesses are those localized in left lobe, multiple, and/or pyogenic abscesses). However, a subset of patients with amoebic liver abscesses remain symptomatic, with a significant risk of rupture of the abscess into the peritoneum. The role of image-guided percutaneous therapeutic aspiration in these patients remains controversial.

### Objectives

To assess the beneficial and harmful effects of image-guided percutaneous procedure plus metronidazole versus metronidazole alone in patients with uncomplicated amoebic liver abscess.

### Search strategy

We searched the *Cochrane Hepato-Biliary Group Controlled Trials Register*, the *Cochrane Central Register of Controlled Trials* in *The Cochrane Library* (Issue 2, 2007), *MEDLINE* (1966 to November 2007), *EMBASE* (1988 to September 2007), and *Science Citation Index Expanded* (1945 to September 2007).

### Selection criteria

Randomised or quasi-randomised trials comparing an image-guided percutaneous procedure plus metronidazole versus metronidazole alone in patients with uncomplicated amoebic liver abscess.

### Data collection and analysis

Inclusion criteria, trial quality assessment, and data extraction were done in duplicate. We calculated relative risks (RR) and mean differences, and checked for heterogeneity by visual inspection of forest plots and chi-squared and $I^2$ tests.

### Main results

Seven low quality randomised trials were included. All studies included a total of 310 patients, but due to selective outcome reporting bias, less patients could be included in our analyses. Pooled analysis of three homogenous trials showed that needle aspiration did not significantly increase the proportion of patients with fever resolution (RR 0.60, 95% confidence interval (CI) 0.22 to 1.61). Sensitivity analysis according to trial quality preserved these findings. Trials that evaluated resolution of abdominal pain, days to resolution of fever, pain, resolution of abscess cavities, reduction in liver size, and duration of hospitalisation were heterogeneous. The benefits in the number of days to resolution of pain (MD -1.59, 95%CI -2.73 to -0.42), number of days to resolution of abdominal tenderness (MD -1.70, 95%CI -2.86 to -0.54), and duration of hospitalisation (MD -1.31, 95%CI -2.05 to -0.57) were observed in the needle aspiration group only.

**Authors' conclusions**

Therapeutic aspiration in addition to metronidazole to hasten clinical or radiologic resolution of uncomplicated amoebic liver abscesses cannot be supported or refuted by the present evidence. The trials lack methodological rigour and adequate sample size to conclude on the presence of effectiveness of adjunctive image-guided aspiration plus metronidazole versus metronidazole alone. Further randomised trials are necessary.

## PLAIN LANGUAGE SUMMARY

**Percutaneous needle aspiration does not seem to help patients with uncomplicated amoebic liver abscesses**

Amoebiasis (disease caused by the protozoan *Entameoba histolytica*) remains an important clinical problem in countries around the world, with 40 to 50 million people affected. Mortality rates are significant, with 40,000 to 110,000 deaths each year. In fact, amoebiasis mortality is second only to malaria as cause of death from protozoan parasites. The most common complication of amoebiasis is the formation of a pus-filled mass inside the liver (liver abscess). Metronidazole is the drug of choice for treatment of amoebic liver abscesses followed by a luminal agent to eradicate the asymptomatic carrier state. Cure rates are 95% with disappearance of fever, pain, and anorexia within 72 to 96 hours. This review compares the standard treatment with a more invasive alternative, where pus-filled mass is drained by image-guided percutaneous procedure (performed through the skin). Seven low quality randomised trials were included. All the seven studies included a total of 310 patients, but due to selective outcome reporting bias, less patients could be included in our analyses. Pooled analysis of three homogenous trials showed that needle aspiration did not significantly increase the proportion of patients with fever resolution. Benefits could be observed in resolution time of pain and tenderness. No additional benefit has been found with percutaneous needle aspiration plus metronidazole *versus* metronidazole alone for uncomplicated amoebic liver abscesses in hastening clinical and radiologic resolution. However, this conclusion is based on trials with methodological flaws and with insufficient sample sizes, and requires further confirmation in larger well-designed, randomised trials.

## BACKGROUND

### *Epidemiology*

Amoebiasis remains an important clinical problem in countries around the world, with 40 to 50 million people affected. Mortality rates are significant, with 40,000 to 110,000 deaths each year. In fact, amoebiasis mortality is second only to malaria as cause of death from protozoan parasites (Hughes 2000; Stanley 2003). Amoebiasis is prevalent in countries where public health and personal hygiene are sub-optimal (Hughes 2000; Stanley 2003). Increasing travelling, immigration of individuals from endemic areas, growth of the homosexual population, and increasing immunosuppression are factors contributing to the increased risk for amoebiasis worldwide (Hughes 2000). Endemic areas are the Indian subcontinent, Southeast Asia, Africa, and South and Central America (Reed 1992).

### *Pathogenesis*

Ingestion of *Entamoeba* (E) *histolytica* cysts through food or water contaminated by human faeces causes amoebiasis. Asymptomatic colonisation of the gastrointestinal tract is common, but some patients develop invasive disease of the colon (Hughes 2000; Stanley 2003). The amoebae can breach the colonic mucosal barrier and travel through the portal circulation to the liver. *E histolytica* blocks intrahepatic portal venules, and proteolytic enzymes digest the parenchymal cells forming a liquefied central area of necrosis, this causes amoebic liver abscesses.

Amoebic liver abscess is the most common extraintestinal manifestation of *E. histolytica* infection. All age groups are affected, but it is 10 times more common in the 20 to 40-year old age group (Ruiz-Palacios 1997; Petri 1999) and 12 times more common in men than women. If left untreated, amoebic liver abscesses can be fatal, with death from sepsis. With early diagnosis and treatment with metronidazole alone, mortality has dropped to less than 1% (Ravdin 1995).

### *Diagnosis*

Ultrasound and computed tomography scans are non-invasive, equally sensitive imaging modalities for the detection of amoebic liver abscesses (Hughes 2000; Stanley 2003), but they cannot specifically differentiate amoebic from pyogenic abscess. Serum antibody detection is an important confirmatory test in the case of amoebic liver abscesses. Serologic tests are about 90% sensitive for amoebic liver abscess, with important limitations within the first week of the disease, and complementary serological assays must be performed (Petri 1999).

### *Treatment*

Metronidazole is the drug of choice for treatment of amoebic liver abscesses followed by a luminal agent to eradicate the asymptomatic carrier state (Hughes 2000). Cure rates are 95% with disappearance of fever, pain, and anorexia within 72 to 96 hours ( Ravdin 1995; Reed 1998). Most abscesses heal from the periphery usually in four weeks after initiating therapy. Mean time to complete radiologic resolution is three to nine months with greater than 50% reduction in liver size within a week (Hughes 2000).

However, approximately 10% to 15% of patients remain symptomatic despite of proper drug treatment. In recent years, imaging-guided percutaneous treatment with needle aspiration or catheter drainage has replaced surgical intervention as the procedure of choice for therapeutically reducing abscess size (Tandon 1997). Simple needle aspiration is less invasive, less expensive, allows for aspiration of multiple abscesses in the same session, and avoids problems related to follow-up catheter care (Giorgio 1995; Tandon 1997). Therapeutic aspiration is the standard of care in complicated liver abscesses, which include those with high risk of abscess rupture; left lobe liver abscesses, because of increased frequency of peritoneal leak or rupture into the pericardium; no response to drug therapy within five to seven days; bacterial co-infection, and uncertainty in diagnosis (Haque 2003; Stanley 2003).

It is important in clinical practice to identify subgroups of patients with amoebic liver abscesses who will benefit from ultrasound- or computed tomography-guided therapeutic aspiration. Spontaneous rupture of the abscess into the peritoneum can occur in 2% to 7% of patients (Ravdin 1995), and mortality rates ranged from 2% to 18% (Sharma 1996). Prediction of rupture is difficult in a setting without a high index of suspicion or without ultrasound monitoring to ascertain changes in the thickness between the skin surface, the liver capsule, and the cavity margin. Existing evidence, however, on the role of image-guided percutaneous therapy is conflicting. Clinical trials are small with debatable results and we have been unable to identify systematic reviews or meta-analyses on this topic. If needle aspiration hastens response to amoebicidal drugs and clinical recovery, this can potentially improve the quality of life, shorten hospital stay, and possibly reduce health care costs especially in developing countries.

## OBJECTIVES

To determine the beneficial and harmful effects of image-guided percutaneous procedure plus metronidazole compared with metronidazole alone in patients with uncomplicated amoebic liver abscess.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

All randomised clinical trials were included in the review regardless of language, blinding, and publication status. In case there were

too few randomised clinical trials, quasi-randomised clinical trials were considered for inclusion in an exploratory analysis to assess adverse events.

### Types of participants

Adult patients admitted to the hospital with a clinical diagnosis of uncomplicated amoebic liver abscesses confirmed by a positive serologic result for *E histolytica* either by enzyme-linked immunosorbent assay (ELISA) or indirect hemagglutination assay (IHA), and with characteristic radiologic features on diagnostic imaging (computed tomography scan or ultrasound) confirming liver abscesses.

The trials that included patients with pyogenic abscesses, impending rupture, and/or other findings suggestive of complicated liver abscess, were not considered in this review.

### Types of interventions

Image-guided percutaneous procedure, either needle aspiration or catheter drainage, plus metronidazole versus metronidazole in a similar dosage and duration alone.

Any collateral interventions if used equally in all intervention groups were allowed.

### Types of outcome measures

***Primary outcomes***

1. Mortality.
2. Proportion of patients without resolution of abscess size on image follow-up.
3. Clinical improvement or response to treatment as follows:

Lack of resolution of fever expressed as:

- proportion of patients remaining febrile;
- days to resolution of fever;

Lack of resolution of pain expressed as:

- proportion of patients without resolution of pain;
- days to resolution of pain;

Lack of resolution of abdominal tenderness expressed as:

- proportion of patients without resolution of tenderness;
- days to resolution of tenderness;
- proportion of patients without reduction in liver size.

***Secondary outcomes***

4. Duration of hospitalisation.

5. Adverse events. Occurrence of complications, that is, rupture of abscess cavity and number of patients requiring surgical intervention.

## Search methods for identification of studies

We searched the following databases: *The Cochrane Hepato-Biliary Group Controlled Trials Register* (Gluud 2008), *The Cochrane Central Register of Controlled Trials* (*CENTRAL*) in *The Cochrane Library* (Issue 2, 2007), *MEDLINE* (1950 to November 2007), *EMBASE* (1980 to September 2007) and *Science Citation Index Expanded* (1945 to September 2007) (Royle 2003). The search strategies are displayed in Appendix 1. We reviewed the reference lists of the retrieved articles for potentially relevant studies, including review articles on the topic. We contacted the corresponding authors of relevant studies identified from the initial search and experts in the field for any information on unpublished articles.

## Data collection and analysis

**Study selection**

Two authors (NC, JH) independently reviewed the search output for potentially relevant trials for inclusion. Two authors (NC, JH) assessed the trials for potential inclusion. We excluded studies that do not meet the inclusion criteria and stated the reason in the 'Characteristics of excluded studies'. Disagreements were settled by discussion with a third co-author (FT). Each trial was assessed for possible multiple publications from the same data set to ensure that each trial is included only once in the review. We contacted the authors of the studies to obtain or verify missing information in the trial.

**Assessment of bias risk by components of methodological quality**

Two authors (NC, JH) independently assessed the bias risk by the following components of methodological quality of included studies (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008):

***Generation of the allocation sequence***

- Adequate, if the allocation sequence was generated by a computer or random number table. Drawing of lots, tossing of a coin, shuffling of cards, or throwing dice were also considered as adequate if a person who was not otherwise involved in the recruitment of participants performed the procedure.
- Unclear, if the trial was described as randomised, but the method used for the allocation sequence generation was not described.
- Inadequate, if a system involving dates, names, or admittance numbers were used for the allocation of patients.

***Allocation concealment***

- Adequate, if the allocation of patients involved a central independent unit, on-site locked computer, identically appearing numbered drug bottles or containers prepared by an independent pharmacist or investigator, or sealed envelopes.
- Unclear, if the trial was described as randomised, but the method used to conceal the allocation was not described.
- Inadequate, if the allocation sequence was known to the investigators who assigned participants or if the study was quasi-randomised.

*Blinding*

- Adequate, if the trial was described as double blind and the method of blinding involved identical placebo or active drugs. Due to the use of image-guided aspiration or catheter drainage as an intervention, we are well aware that it may be very difficult to properly blind such trials.
- Unclear, if the trial was described as double blind, but the method of blinding was not described.
- Not performed, if the trial was not double blind.

*Follow-up*

- Adequate, if the numbers and reasons for dropouts and withdrawals in all intervention groups were described or if it was specified that there were no dropouts or withdrawals.
- Unclear, if the report gave the impression that there had been no dropouts or withdrawals, but this was not specifically stated.
- Inadequate, if the number or reasons for dropouts and withdrawals were not described.

Furthermore, we registered whether or not the randomised clinical trials used 'intention-to-treat' analysis (Gluud 2001) and sample size calculation.

Any disagreement was resolved by discussion and settled by a third author (FT). We contacted the trial author for clarification as necessary.

**Data extraction**

Two authors (NC, JH) independently extracted data for each of the outcomes from each relevant study using a pre-designed data extraction form. We extracted the following information on study characteristics: population studied, interventions performed, and outcomes evaluated. These include trial setting, criteria for inclusion and exclusion of participants, details on interventions performed including dose of medications, duration of treatment, and co-interventions. Outcome measures to be extracted included mortality, symptom resolution, radiologic resolution of abscess cavity, and length of hospital stay. We also extracted adverse events reported such as occurrence of complications, non-responders, and those needing surgical intervention.

**Data analysis**

Data were entered in Review Manager Version 5.0 (RevMan 2008) by one author (NC) and checked by two other authors (JH, FT). Continuous outcomes were expressed as mean differences with 95% confidence intervals while dichotomous outcomes were expressed as relative risks with a 95% CI. For each outcome we extracted the number of participants assigned to each group and whenever possible extracted data to allow for an intention-to-treat analysis. If the number randomised and the numbers analysed were inconsistent, we reported this as the percentage lost to follow-up. For binary outcomes, the number of participants experiencing the event in each group was recorded. For continuous outcomes, the arithmetic means and standard deviations for each group were extracted. Any disagreement was resolved by discussion with reference to the trial report and resolution by a co-author (FT). For outcomes for which data were not reported or were reported in a different format, we contacted the authors for clarification. We checked for heterogeneity among trials by visual inspection of the forest plots and by using the chi-squared and $I^2$ tests for heterogeneity (Higgins 2008), using a P-value less than 0.10 as the cut-off level for statistically significant heterogeneity. When heterogeneity was detected, potential sources of heterogeneity according to intervention, participants, trial setting, and trial quality were explored. We conducted subgroup analyses according to study quality and subgroup analysis according to type of percutaneous procedure where sufficient data were available. We analysed data by both the fixed-effect model analysis and random-effects model analysis, but we only reported the former in the text if the outcome of both analyses were the same. Outcomes were analysed as reported in the trial, that is, either per protocol or as intention-to-treat analysis.

# RESULTS

## Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

A total of 124 studies were retrieved from the broad search strategies used. After the elimination of editorials, reviews, and repeated reports, seven trials met the inclusion criteria, and 31 studies were excluded from inclusion in this review. The 31 excluded studies with details on why they failed to meet the inclusion criteria are outlined in the table of 'Characteristics of excluded studies'. Details of the seven included trials are outlined in the table of 'Characteristics of included studies'. All seven trials were published in English. The number of participants per trial ranged from 29 to 52 participants. Unfortunately a detailed description of included participants (eg, anatomical considerations, serological status, and a precise definition of disease status) was not provided and limits the overview of the included population.

Considering the lack of a clear definition of large abscess in the included studies, the magnitude of the abscess was diverse. In the Blessman 2003 et al trial, abscess larger than 10 cm were excluded, but in all other trials no information on the size of the abscess was stated. Additionally, a significant difference on the abscess size among groups was observed in the trial by Sharma 1989 et al, and some information about the size was provided in de la Rey Nel 1989. Most of the trials involved abscess within the range of 6 cm to 8 cm.

**Population studied**

Six trials were performed in developing countries where amoebic liver abscesses are prevalent and one trial was performed in

the United States (Van Allan 1992). All trials involved a total of 310 patients diagnosed with uncomplicated amoebic liver abscess based on clinical, serologic, and radiologic criteria. The mean age ranged from 35 to 46 years, with the majority of trials involving a greater number of males than females.

**Description of interventions**

Five trials employed ultrasound-guided aspiration of the abscess cavities by needle aspiration (de la Rey Nel 1989; Sharma 1989; Arredondo 1993; Tandon 1997; Blessman 2003) and two trials by insertion of a temporary catheter (Widjaya 1991; Van Allan 1992). In all trials, aspiration or drainage of the abscess cavities were performed until drainage ceased. All trials but two evaluated oral metronidazole in doses ranging from 750 mg to 800 mg three times a day over ten days. de la Rey Nel 1989 et al trial administered the drug for five days and Van Allan 1992 et al trial administered the drug for a period of three weeks. Three trials administered other luminal amoebicidal drugs as co-interventions in addition to metronidazole; that is, dehydroemetine (Arredondo 1993), iodoquinol (Van Allan 1992), and chloroquine (Widjaya 1991).

**Outcome assessment**

All trials but Widjaya 1991 measured clinical improvement in terms of fever lysis and resolution of abdominal pain as outcomes. Analysis of fever resolution was precluded in two trials due to incomplete reporting (Arredondo 1993; Blessman 2003). Three trials reported clinical improvement as resolution of symptoms on a daily basis (de la Rey Nel 1989) and based on a graded scale measuring severity (Van Allan 1992; Tandon 1997). The latter two trials assessed symptom resolution as a reduction from baseline level. Data from Van Allan 1992; Tandon 1997 were reported as continuous data. One trial reported on fever lysis (Sharma 1989), and one reported resolution of abdominal pain as proportions of patients experiencing symptom resolution (Blessman 2003). Two trials reported the number of days to resolution of abdominal tenderness as an outcome (de la Rey Nel 1989; Tandon 1997), and one trial reported the proportion of patients demonstrating a reduction in liver size (Sharma 1989). One trial evaluated radiologic resolution of the abscess size by serial ultrasonographic monitoring and reported these outcomes as proportions of patients with radiologic resolution of abscess cavities (Sharma 1989). Three trials measured duration of hospitalisation as an outcome (Van Allan 1992; Arredondo 1993; Tandon 1997). Five of the eight trials reported adverse events (de la Rey Nel 1989; Sharma 1989; Widjaya 1991; Van Allan 1992; Arredondo 1993), but the report was incomplete, precluding analysis.

## Risk of bias in included studies

The included trials varied in methodological quality, which in general was low (Figure 1; Figure 2). A description of the methodological quality of each of the included trials is given in the table of 'Characteristics of included studies'. All trials failed to report randomisation procedures in sufficient detail (and additional information was not provided). Only one trial was considered to have adequate allocation concealment (Van Allan 1992). Allocation concealment was unclear in five trials (de la Rey Nel 1989; Sharma 1989; Widjaya 1991; Tandon 1997; Blessman 2003). In one trial, the methodological quality was not possible to be clearly determined (Arredondo 1993). Blinding of outcome assessment was unclear in six trials (de la Rey Nel 1989; Sharma 1989; Widjaya 1991; Arredondo 1993; Tandon 1997; Blessman 2003) and not blinded in one trial (Van Allan 1992). All trials reported a per-protocol analysis. Four trials reported number of participants lost to follow-up (de la Rey Nel 1989; Sharma 1989; Widjaya 1991; Blessman 2003), and three trials did not specify whether there was any lost to follow-up (Van Allan 1992; Arredondo 1993; Tandon 1997). It was observed an important heterogeneity in the outcomes reported, which is an important limitation to pool the trials as their result will be highly biased.

**Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.**

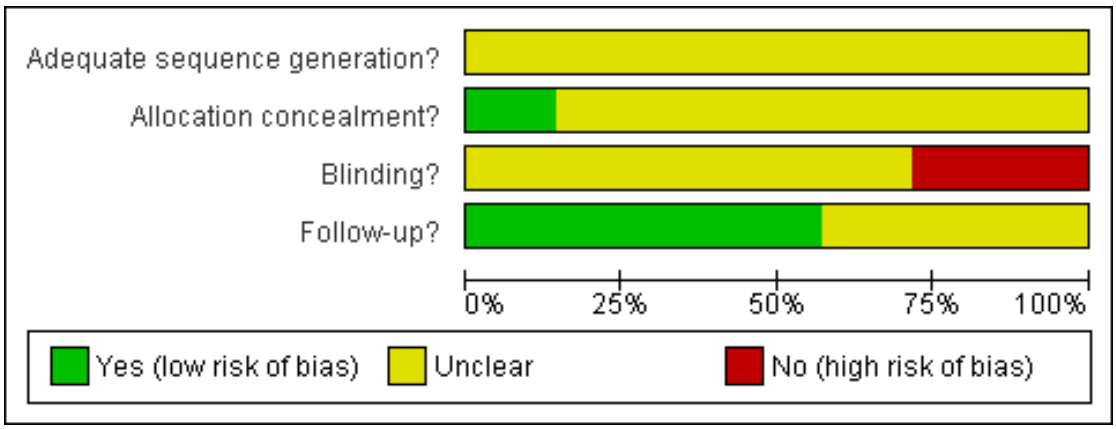
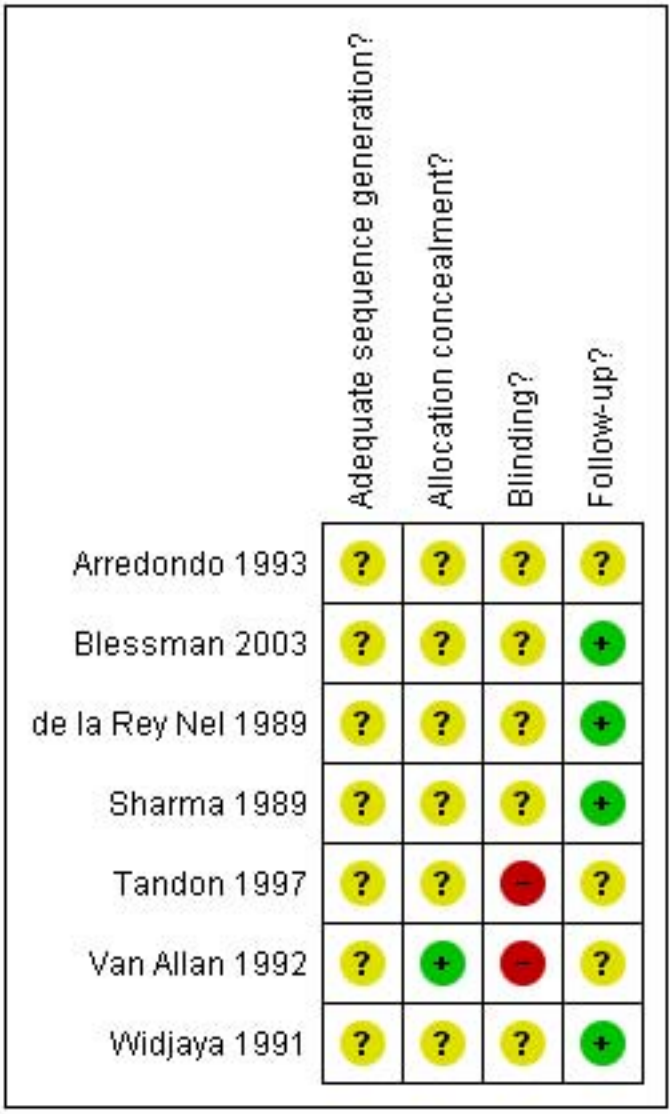


**Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.**



## Effects of interventions

The results of the included trials are described in the table of 'Data and analyses' and are described below.

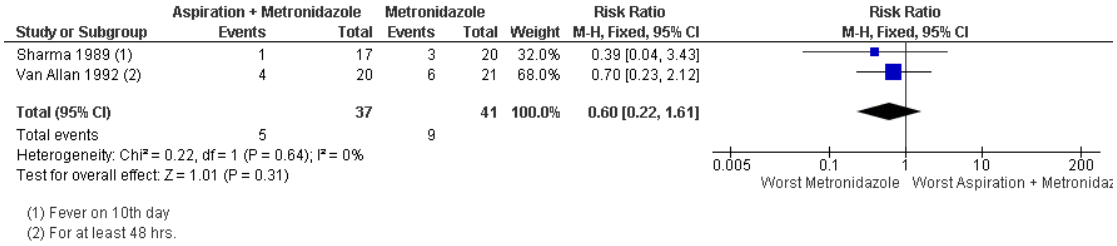
**Mortality**

Van Allan 1992 et al reported that there were no deaths. The other six trials did not report any data on deaths.

**Proportion of patients remaining febrile**

Two trials reported the number of patients remaining febrile as an outcome, with an aggregate sample size of 78 patients (aspiration plus metronidazole = 37, and metronidazole = 41) (Sharma 1989; Van Allan 1992). The study population, methods of intervention, and outcomes measured in these two trials were similar enough in order to combine them in a meta-analysis. No statistical heterogeneity was found with a Chi square = 0.22, df = 1, P = 0.64, $I^2$ = 0%. The relative risk is 0.60 (95% CI 0.22 to 1.61), showing no evidence of a statistical difference between aspiration and no aspiration Figure 3.

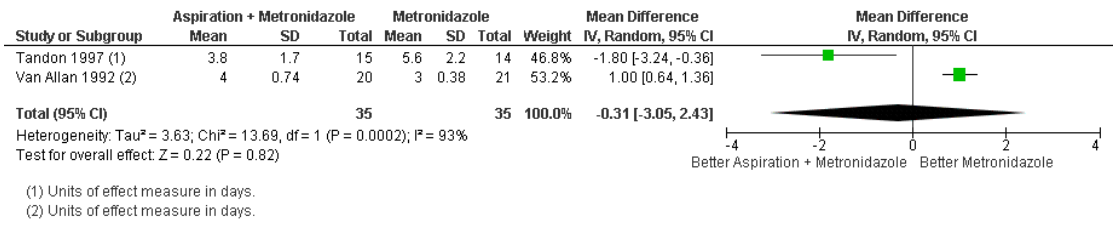
**Figure 3. Forest plot of comparison: 1 Needle aspiration and metronidazole versus metronidazole alone, outcome: 1.1 Proportion of patients remaining febrile.**




**Days to resolution of fever**

Two trials with an aggregate sample size of 70 patients (aspiration plus metronidazole = 35, metronidazole = 35) reported this outcome (Van Allan 1992; Tandon 1997). When data from these two trials were pooled, a statistically significant heterogeneity was noted (Chi square = 13.69, df = 1, P = 0.0002, $I^2$ = 92.7%), and no statistical difference was observed Figure 4.

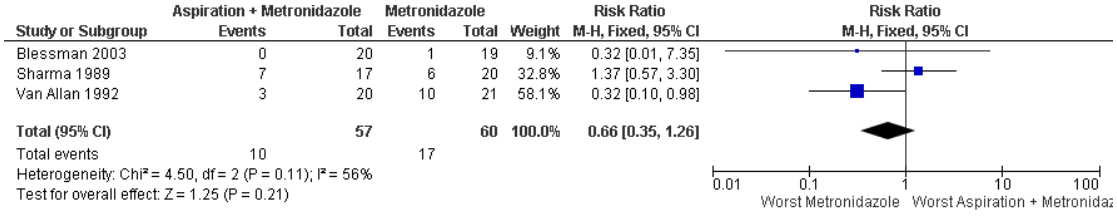
**Figure 4. Forest plot of comparison: 1 Needle aspiration and metronidazole versus metronidazole alone, outcome: 1.2 Days to resolution of fever.**



**Proportion of patients without resolution of pain**

Three trials reported this outcome with an aggregate sample size of 117 patients (metronidazole = 60, aspiration = 57) (Sharma 1989; Van Allan 1992; Blessman 2003). The pooled relative risk showed a tendency towards favouring aspiration 0.66 (95% CI 0.35 to 1.26) in terms of resolution of abdominal pain, although this was not found to be statistically significant. A medium level of heterogeneity was noted with a Chi square = 4.50, df = 2, P = 0.11, $I^2$ = 56% Figure 5.

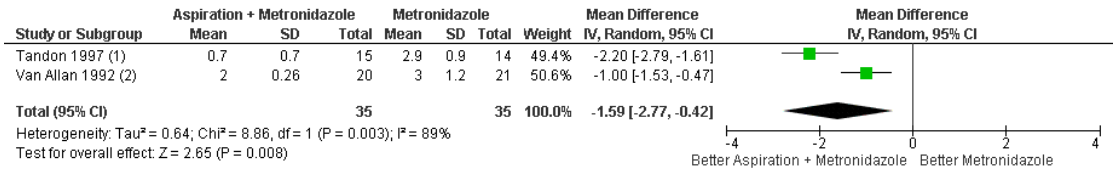
**Figure 5. Forest plot of comparison: 1 Needle aspiration and metronidazole versus metronidazole alone, outcome: 1.3 Proportion of patients without resolution of pain.**




**Days to resolution of pain**

Two trials (Van Allan 1992; Tandon 1997) with an aggregate sample size of 70 patients (metronidazole = 35, aspiration = 35) reported this outcome. When data from these trials were pooled, a statistically significant heterogeneity was found (Chi square = 10.04, df = 1, P = 0.002 $I^2$ = 90%), and a reduction in the number of days to resolution of pain was observed in the needle aspiration group (MD -1.59, 95% CI -2.73 to -0.42) Figure 6, but with the few trials available, the subgroup analyses was not performed in order to explain the heterogeneity.

**Figure 6. Forest plot of comparison: 1 Needle aspiration and metronidazole versus metronidazole alone, outcome: 1.4 Days to resolution of pain.**

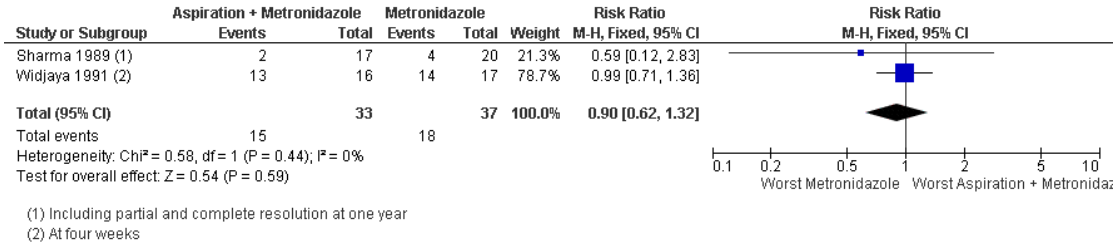



(1) Units of effect measure in days.
(2) Units of effect measure in days.

**Proportion of patients without resolution of abscess size**

Two trials monitored resolution of abscess size by serial ultrasonographic monitoring with an aggregate sample size of 70 participants (metronidazole = 37, aspiration = 33) (Sharma 1989; Widjaya 1991). When data for this outcome were pooled, heterogeneity was not noted (Chi square = 0.58, df = 1, P = 0.44, $I^2$ = 0%). The pooled relative risk is of 0.90 (95% CI 0.62 to 1.32), showing no significant difference between needle aspiration and metronidazole alone Figure 7.

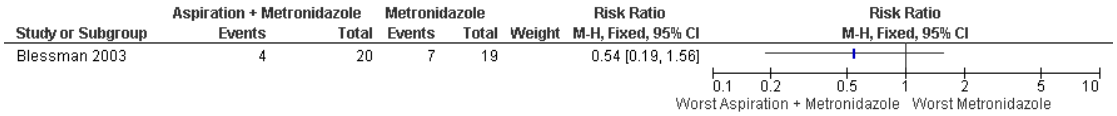
**Figure 7. Forest plot of comparison: 1 Needle aspiration and metronidazole versus metronidazole alone, outcome: 1.5 Proportion of patients without resolution of abscess size.**




**Proportion of patients without resolution of abdominal tenderness**

One trial reported this outcome with a relative risk of 0.54 (95% CI 0.19 to 1.56) with a sample size of 39 participants (aspiration plus metronidazole = 20, metronidazole = 19) (Blessman 2003) Figure 8.

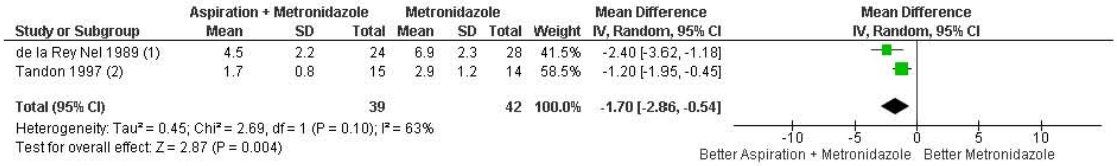
**Figure 8. Forest plot of comparison: 1 Needle aspiration and metronidazole versus metronidazole alone, outcome: 1.6 Proportion of patients without resolution of abdominal tenderness.**




**Days to resolution of abdominal tenderness**

Two trials with an aggregate sample size of 81 patients (aspiration plus metronidazole = 39, metronidazole = 42) reported this outcome (de la Rey Nel 1989; Tandon 1997). When data for these two trials were pooled, statistical heterogeneity was found (Chi square = 2.69, df = 1, P = 0.10, $I^2$ = 62.8), and a reduction in the number of days to resolution of abdominal tenderness was observed in the needle aspiration group (MD -1.70, 95% CI -2.86 to -0.54) Figure 9, but with the few trials available, the subgroup analyses was not performed in order to explain the heterogeneity.

**Figure 9. Forest plot of comparison: 1 Needle aspiration and metronidazole versus metronidazole alone, outcome: 1.7 Days to resolution of abdominal tenderness.**

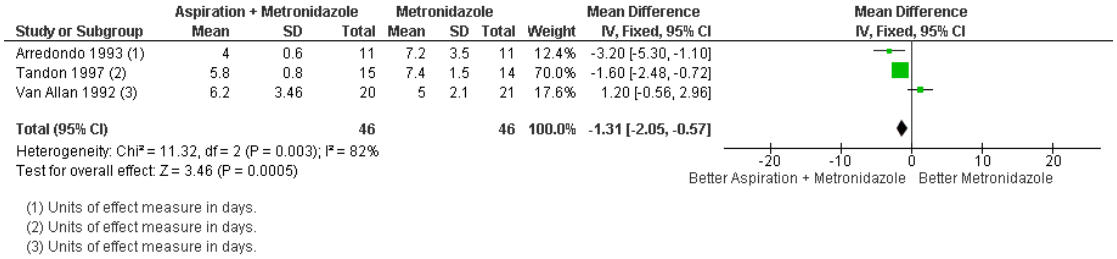



(1) Units of effect measure in days.
(2) Units of effect measure in days.

**Duration of hospitalisation**

Three trials reported this outcome with an aggregate sample size of 92 patients (Van Allan 1992; Arredondo 1993; Tandon 1997). The results of Arredondo 1993 and Tandon 1997 were not consistent with the Van Allan 1992 trial, favouring metronidazole treatment alone. When data for these three trials were pooled, a medium level of heterogeneity (Chi square = 11.32, df = 2, P = 0.003, $I^2$ = 82%) was detected, and a reduction in the duration of hospitalisation was observed in the needle aspiration group (MD -1.31, 95% CI -2.05 to -0.57) Figure 10, but with the few trials available, the subgroup analyses was not performed in order to explain the heterogeneity.

**Figure 10. Forest plot of comparison: 1 Needle aspiration and metronidazole versus metronidazole alone, outcome: 1.8 Duration of hospitalisation.**

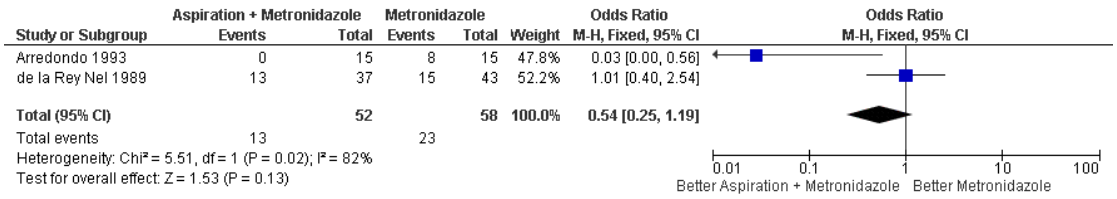



**Adverse events**

***Number of patients requiring surgical intervention and rupture of abscess cavity***

Two trials reported adverse events as proportion of non-responders to initial intervention (de la Rey Nel 1989; Arredondo 1993). When data from these two trials were meta-analysed, a statistically significant heterogeneity was noted (Chi square = 7.84, df = 1, P = 0.02, $I^2$ = 82%) and no difference was observed between the groups Figure 11. Only in one trial, five patients underwent surgical intervention (there were no data to which group the patients belonged) (Widjaya 1991). Only one trial reported a single case of abscess rupture in the non-aspirated group (de la Rey Nel 1989). However, reporting in the other trials was incomplete, precluding an analysis for this outcome.

**Figure 11. Forest plot of comparison: 1 Needle aspiration and metronidazole versus metronidazole alone, outcome: 1.9 Proportion of non-responders.**



## DISCUSSION

The decision to therapeutically decrease abscess size in uncomplicated amoebic liver abscess is an area of controversy and we address this issue in our review. We found no evidence that image-guided needle aspiration provides added benefits in the management of uncomplicated amoebic liver abscess. However, small study populations, inadequate methods to minimize bias, and significant heterogeneity made interpretation of pooled estimates problematic. Most of the trials included in this review were performed in the late 1980s and early 1990s in low-income countries where amoebic liver abscesses are endemic. Evidence shows that the quality of randomised clinical trials affects estimates of intervention efficacy, which is significantly exaggerated in low-quality trials. Kjaergard et al reported the association between trial quality, trial setting, and year of publication (Kjaergard 1999). Most of the trials included in the present review failed to incorporate methodological procedures, which restrict bias. This lack of rigorousness may bias estimates of treatment effect. Inadequate sample size, unclear methods of generation of allocation sequence to ensure adequacy of randomisation, inability to conceal treatment allocation, and lack of blinding allow exaggeration of treatment efficacy when results of these high-risk bias trials are meta-analysed. To minimise bias, adequate methodological approaches in trial design, conduct, and reporting of results when assessing therapy of amoebic liver abscesses are needed to obtain robust conclusions. However, the clinical expertise and knowledge about the intrinsic limitations of statistic inferences must be another important tool to interpret the available information (Guller 2008).

In addition, significant heterogeneity has cast doubt on the robustness of conclusion drawn from these trials. Possible sources for heterogeneity in this review are variability in timing of outcome assessment, variability in definition of outcomes to be assessed, presence of co-interventions, and differences in the general quality of care received as a consequence of trial setting. Trials varied in defining the most relevant clinical outcome, ie, is it symptomatic improvement or is it radiologic resolution. Improvement in symptoms is no doubt important; however, these symptoms have to be clearly defined and timing of assessment must be uniformly evaluated.

Furthermore, it is equally important to study hard clinical outcomes, such as mortality and adverse events related to the treatment intervention, which can greatly influence treatment success. However, other outcomes, albeit more subjective, are more likely to be impacted upon by the experimental therapy, as observed in the analyses on resolution of pain and tenderness. Drug-related adverse events, as well as treatment-related complications as a result of invasive procedures, such as needle aspiration, were not explored in greater detail in the trials included in this review.

This lack of uniformity and inadequate methodological approach in clinical evaluation reflect the lack of standardisation in the therapeutic approach to amoebic liver abscesses. The creation of a diagnostic and therapeutic algorithm for amoebic liver abscesses may contribute to create this much-needed uniformity in therapy and the potential to give rise to well-designed clinical trials in the future.

## AUTHORS' CONCLUSIONS

### Implications for practice

This review found no evidence to support or refute aspiration of the abscess cavity plus metronidazole versus metronidazole alone in uncomplicated amoebic liver abscess. Trials were, however, small and lacked methodological rigour for us to be able to conclude that aspiration does or does not benefit patients. Accordingly, our findings are inconclusive to make a definite recommendation on the benefit of adjunctive therapeutic needle aspiration.

### Implications for research

Randomised clinical trials with larger sample sizes and adequate randomisation (generation of the allocation sequence as well as allocation concealment) and blinded outcome assessment of outcomes important to patients are urgently needed. Such trials should use uniform measures to assess outcomes.

Strict evaluation of adverse events resulting from different interventions employed in the management of amoebic liver abscesses should be included in future trials. Furthermore, trials ought to be reported according to the recommendations of the CONSORT statement.

## ACKNOWLEDGEMENTS

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Peer Reviewers: A Merens, France; NA Deepak, India.

Contact Editor: C Gluud, Denmark.

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* *Indicates the major publication for the study*

# CHARACTERISTICS OF STUDIES

## Characteristics of included studies *[ordered by study ID]*

**Arredondo 1993**

| | |
|---|---|
| Methods | Randomised trial.<br>Generation of the allocation sequence: Unclear. No information provided.<br>Allocation concealment: Unclear. No information provided.<br>Blinding: Unclear. No information provided.<br>ITT analysis: No.<br>Follow-up: No information provided.<br>Sample size calculation: No information provided. |
| Participants | Country: Mexico.<br>Number of participants randomised: 22.<br>Inclusion criteria: Right upper quadrant abdominal pain, fever, increased white blood counts, and suggesting image by ultrasound.<br>Exclusion criteria: Pleuropulmonary and pericardial complications, sever liver failure, abdominal guarding, shock or previous medical therapy. |
| Interventions | Experimental: US guided aspiration plus metronidazole 750 mg TID, and dehydroemetine 1-1.5 mg/kg/day.<br>Control: Metronidazole 750 mg TID, and dehydroemetine 1 to 1.5 mg/kg/day. |
| Outcomes | Fever, white blood count, pain, hospitalisation time. |
| Notes | Data obtained from abstract.<br>The authors were not able to send the complete manuscript, to include all data. |

***Risk of bias***

| **Item** | **Authors' judgement** | **Description** |
|---|---|---|
| Adequate sequence generation? | Unclear | No information provided. |
| Allocation concealment? | Unclear | No information provided. |
| Blinding?<br>All outcomes | Unclear | No information provided. |
| Follow-up? | Unclear | No information provided. |

**Blessman 2003**

| | |
|---|---|
| Methods | Randomised trial.<br>Generation of the allocation sequence: Unclear. No information provided.<br>Allocation concealment: Unclear. No information provided.<br>Blinding: Unclear. No information provided.<br>ITT analysis: No information provided.<br>Follow-up: 28 days after discharge, all patients were re-examined at the end of the follow-up period.<br>Sample size calculation: No information provided. |
| Participants | Country: Vietnam<br>Number of participants randomised: 39.<br>Inclusion criteria: Abscess with a diameter of 6 cm to 10 cm; abscess localisation in the right liver lobe, except the caudate lobe; age >18 years.<br>Exclusion criteria: Treatment with amoebicidal drugs before hospital admission, pregnancy, or presence of aerobic or anaerobic bacteria in the abscess fluid. |
| Interventions | Experimental: Fine needle US guided aspiration plus metronidazole 30 mg/kg TID for 10 days.<br>Control: Metronidazole 30 mg/kg TID for 10 days. |
| Outcomes | Body temperature, pain and tenderness in right upper abdomen, leucocyte count, erythrocyte sedimentation rate, haemoglobin, and C-reactive protein and abscess volume. |
| Notes | |

***Risk of bias***

| **Item** | **Authors' judgement** | **Description** |
|---|---|---|
| Adequate sequence generation? | Unclear | No information provided. |
| Allocation concealment? | Unclear | No information provided. |
| Blinding?<br>All outcomes | Unclear | No information provided. |
| Follow-up? | Yes | 28 days after discharge, all patients were re-examined at the end of the follow-up period. |

**de la Rey Nel 1989**

| | |
|---|---|
| Methods | Randomised trial.<br>Generation of the allocation sequence: Unclear.<br>Allocation concealment: Unclear. No information provided.<br>Blinding: No information provided.<br>ITT analysis: No information provided.<br>Follow-up: Monthly until complete resolution of the cavity, all patients were re-examined at the end of the follow-up period.<br>Sample size calculation: No information provided. |
| Participants | Country: South Africa.<br>Number of participants randomised: 80.<br>Inclusion criteria: Liver abscess by ultrasound and positive amoebiasis gel diffusion test.<br>Exclusion criteria: Refuse to be hospitalised, liver abscess located in the superior half of the left lobule. |
| Interventions | Experimental: US guided aspiration plus metronidazole 800 mg TID for 5 days.<br>Control: Metronidazole 800 mg TID for 5 days. |
| Outcomes | Body temperature, tenderness, liver size, and size of abscess cavity. |
| Notes | |

***Risk of bias***

| **Item** | **Authors' judgement** | **Description** |
|---|---|---|
| Adequate sequence generation? | Unclear | No information provided. |
| Allocation concealment? | Unclear | No information provided. |
| Blinding?<br>All outcomes | Unclear | No information provided. |
| Follow-up? | Yes | Monthly until complete resolution of the cavity, all patients were re-examined at the end of the follow-up period. |

**Sharma 1989**

| | |
|---|---|
| Methods | Randomised case-control trial.<br>Generation of the allocation sequence: No information provided.<br>Allocation concealment: No information provided.<br>Blinding: Unclear.<br>ITT analysis: No.<br>Follow-up: 12 months, all patients were re-examined at the end of the follow-up period.<br>Sample size calculation: No information provided. |
| Participants | Country: India.<br>Number of participants randomised: 39.<br>Inclusion criteria: Positive serological results for *E histolytica* (ELISA and indirect hemagglutination), one or more lesions occupying space in the right lobe of the liver with characteristic features of amoebic liver abscess on ultrasound examination.<br>Exclusion criteria: Abscess in the left lobe, multiple liver abscesses, and impending rupture. |
| Interventions | Experimental: Needle aspiration plus metronidazole 2.4 g at day for 10 days.<br>Control: Metronidazole 2.4 g at day for 10 days. |
| Outcomes | Abdominal pain, fever, anorexia, and hepatomegaly. |
| Notes | |

***Risk of bias***

| **Item** | **Authors' judgement** | **Description** |
|---|---|---|
| Adequate sequence generation? | Unclear | No information provided. |
| Allocation concealment? | Unclear | No information provided. |
| Blinding?<br>All outcomes | Unclear | No information provided. |
| Follow-up? | Yes | 12 months, all patients were re-examined at the end of the follow-up period. |

**Tandon 1997**

| | |
|---|---|
| Methods | Randomised trial.<br>Generation of the allocation sequence: Unclear. No information provided.<br>Allocation concealment: Unclear. No information provided.<br>Blinding: Patient and provider not blinded.<br>ITT analysis: No information provided.<br>Follow-up: No information provided.<br>Sample size calculation: No information provided. |
| Participants | Country: India.<br>Number of participants randomised: 29.<br>Inclusion criteria: uncomplicated, amoebic liver abscess larger than 5 cm.<br>Exclusion criteria: No information provided. |
| Interventions | Experimental: Needle aspiration plus metronidazole 800 mg TID for 10 days.<br>Control: metronidazole alone. |
| Outcomes | Resolution of fever, pain, duration of hospital stay. |
| Notes | Data obtained from abstract.<br>The authors were not able to send the complete manuscript, to include all data. Not information about dose in control group was provided. |

***Risk of bias***

| **Item** | **Authors' judgement** | **Description** |
|---|---|---|
| Adequate sequence generation? | Unclear | No information provided. |
| Allocation concealment? | Unclear | No information provided. |
| Blinding?<br>All outcomes | No | Patient and provider not blinded. |
| Follow-up? | Unclear | No information provided. |

**Van Allan 1992**

| | |
|---|---|
| Methods | Randomised trial.<br>Generation of the allocation sequence: Unclear.<br>Allocation concealment: Adequate. Using sealed envelopes.<br>Blinding: No.<br>ITT analysis: No.<br>Follow-up: No information provided.<br>Sample size calculation: No information provided. |
| Participants | Country: United States.<br>Number of participants randomised: 41.<br>Inclusion criteria: Abscess at least 5 cm in diameter (US or CT), and/or abscess less than 5 cm in diameter accompanied by moderate or severe pain, and/or abscess less than 5 cm in diameter accompanied by fever (>102°F).<br>Exclusion criteria: Inability to obtain informed consent, rupture at the time of diagnosis, contraindication to one or both of the therapeutic regimens, or identification of patients more than 24 hours after initiation of therapy. |
| Interventions | Experimental: US or CT guided needle aspiration plus metronidazole 750 mg TID +/- iodoquinol for 10 to 14 days.<br>Control: Metronidazole 750 mg TID +/- iodoquinol for 10 to 14 days. |
| Outcomes | Temperature, pain, tenderness, and length of hospitalisation. |
| Notes | |

***Risk of bias***

| **Item** | **Authors' judgement** | **Description** |
|---|---|---|
| Adequate sequence generation? | Unclear | No information provided. |
| Allocation concealment? | Yes | Using a sealed-envelope procedure. |
| Blinding?<br>All outcomes | No | From randomisation status could not be obscured from the medical staff. |
| Follow-up? | Unclear | No information provided. |

**Widjaya 1991**

| | |
|---|---|
| Methods | Randomised trial.<br>Generation of the allocation sequence: Unclear.<br>Allocation concealment: Unclear.<br>Blinding: Unclear.<br>ITT analysis: No.<br>Follow-up: Until resolution of abscesses, all patients were re-examined at the end of the follow-up period.<br>Sample size calculation: No information provided. |
| Participants | Country: Indonesia.<br>Number of participants randomised: 60.<br>Inclusion criteria: Symptoms and signs, positive indirect hemagglutination test and suggestive ultrasound findings.<br>Exclusion criteria: No information provided. |
| Interventions | Experimental: Metronidazole 750 mg TID, and chloroquine (500 mg BID the first day, after 500 mg) for 10 days plus US guided aspiration.<br>Control: Metronidazole 750 mg TID, and chloroquine (500 mg BID the first day, after 500 mg at day) for 10 days. |
| Outcomes | Resolution of abscess. |
| Notes | A clear definition of "resolution of abscess" was not provided. |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Adequate sequence generation? | Unclear | No information provided. |
| Allocation concealment? | Unclear | No information provided. |
| Blinding?<br>All outcomes | Unclear | No information provided. |
| Follow-up? | Yes | 56 days, until resolution of abscesses, all patients were re-examined at the end of the follow-up period. |

ITT = intention to treat
US = ultrasound
BID = twice-daily dosage
TID = thrice-daily dosage
CT = computed tomography

## Characteristics of excluded studies *[ordered by study ID]*

| | |
|---|---|
| Bhatia 1998 | A randomised trial comparing metronidazole *versus* secnidazole in 32 patients with amoebic liver abscess. There was no comparison made with percutaneous needle aspiration. |
| Cervantes 1974 | A clinical trial evaluating the use of estrogens in the treatment of amoebic liver abscess. |
| Cohen 1975 | A randomised trial including 36 patients with amoebic liver abscess comparing metronidazole and chloroquine for the treatment of amoebic liver abscess. No comparison was made with percutaneous needle aspiration. |
| Datta 1974 | A controlled clinical trial comparing emetine hydrochloride, niridazole, and metronidazole in the treatment of amoebic liver abscess. No comparison was made with percutaneous needle aspiration. |
| Esquivel Lopez 1979 | This study is non-randomised. Sixty patients with complicated amoebic liver abscesses failing medical therapy received different pharmacologic interventions. No comparison made with percutaneous procedures. |
| Filice 1992 | This study is a retrospective observational study of 51 patients with amoebic liver abscess comparing medical therapy with nitroimidazole, open surgical drainage, and percutaneous drainage followed by intralesional nitroimidazole administration. |
| Freeman 1990 | This study is quasi randomised, without information about adverse events. |
| Genadieva 1997 | A clinical study examining fine needle aspiration biopsy of diffuse liver lesions including non-amoebic hepatic lesions. No comparison was made with medical therapy. |
| Hatchuel 1975 | A randomised, double blind trial comparing tinidazole with metronidazole in 14 patients with amoebic liver abscess. No comparison was made with percutaneous needle aspiration. |
| Irusen 1992 | A prospective cohort study investigating the prevalence and natural history of asymptomatic intestinal colonisation in 50 patients with amoebic liver abscess. |
| Islam 1978 | A randomised trial comparing two medical treatment, tinidazole and metronidazole, in 31 patients with hepatic amoebiasis. No comparison was made with percutaneous needle aspiration. |
| Jain 1990 | A study of 33 patients with hepatopulmonary amoebiasis which compared the efficacy of dehydroemetine and metronidazole. No comparison was made with percutaneous needle aspiration. |
| Jayawickrema 1975 | A randomised trial comparing metronidazole with emetine and chloroquine in the treatment of hepatic amoebiasis. No comparison was made with percutaneous needle aspiration. |
| Khokhani 1977 | A randomised trial comparing the efficacy of tinidazole and metronidazole in 20 patients with amoebic liver abscess. No comparison was made with percutaneous needle aspiration. |
| Khokhani 1978 | A randomised trial of 20 patients with amoebic liver abscess comparing tinidazole and metronidazole. No comparison was made with percutaneous needle aspiration. |

(*Continued*)

| | |
|---|---|
| Lasserre 1983 | A randomised double blind trial evaluating the efficacy of single-day treatment with either ornidazole or tinidazole in 72 patients with amoebic liver abscess. No comparison was made with percutaneous needle aspiration. |
| Mogollon 1999 | Prospective, non-randomised study, in 170 patients, with a high proportion of puncture procedure (n=131). No outcomes were compared. |
| Morales 1975 | A randomised, double blind comparison of intravenous metronidazole and intramuscular emetine in acute amoebic liver abscess. No comparison was made with percutaneous needle aspiration. |
| N'Gbesso 1993 | Non-randomised study, assessing medical treatment, ultrasound-guided puncture and surgical puncture. |
| Powell 1965 | A clinical trial evaluating dehydroemetine in the treatment of amoebic liver abscess. No comparison was made with percutaneous needle aspiration. |
| Powell 1967 | A randomised trial comparing dehydroemetine and emetine hydrochloride in identical dosage in amoebic liver abscess. No comparison was made with percutaneous needle aspiration. |
| Powell 1974 | A clinical trial of benzoyl metronidazole suspension in the treatment of amoebic dysentery and amoebic liver abscess. No comparison was made with percutaneous needle aspiration. |
| Rajak 1998 | A randomised trial including 50 patients with mixed amoebic and pyogenic liver abscesses who received either percutaneous needle aspiration or catheter drainage. No comparison was made to medical treatment alone. |
| Ramani 1993 | Prospective non-randomised study, in 200 patients with ultrasound and serologic diagnosis of liver abscess. The 6-months response was not different among groups. |
| Ruas 1973 | A comparative study of the effects of a novel anti-amoebic drug (RO 7-020) *versus* metronidazole in amoebic liver abscess. No comparison was made with percutaneous needle aspiration. |
| Satpathy 1988 | A randomised trial comparing intravenous metronidazole and intramuscular dehydroemetine in amoebic liver abscess. |
| Simjee 1985 | A randomised trial of metronidazole *versus* tinidazole in 48 patients with amoebic liver abscess. No comparison was made with percutaneous needle aspiration. |
| Singh 1989 | A randomised trial including 50 patients with drug resistant amoebic liver abscess who received a repeat trial of conservative therapy, needle aspirations, percutaneous catheter drainage, and open surgical drainage. |
| Soh 1980 | A randomised trial comparing ornidazole verus tinidazole in patients with amoebic liver abscess. No comparison was made with percutaneous needle aspiration. |
| Yu 2004 | A randomised trial comparing continuous catheter drainage and intermittent needle aspiration in 64 patients with pyogenic liver abscesses. |

(*Continued*)

| | |
|---|---|
| Zafar 2002 | This study is non-randomised. Forty-six patients with amoebic liver abscess received needle aspiration with antiamebic drug treatment *versus* drug treatment alone, based on size of the abscess. |

## DATA AND ANALYSES

### Comparison 1. Needle aspiration and metronidazole versus metronidazole alone

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Proportion of patients remaining febrile | 2 | 78 | Risk Ratio (M-H, Fixed, 95% CI) | 0.60 [0.22, 1.61] |
| 2 Days to resolution of fever | 2 | 70 | Mean Difference (IV, Random, 95% CI) | -0.31 [-3.05, 2.43] |
| 3 Proportion of patients without resolution of pain | 3 | 117 | Risk Ratio (M-H, Fixed, 95% CI) | 0.66 [0.35, 1.26] |
| 4 Days to resolution of pain | 2 | 70 | Mean Difference (IV, Random, 95% CI) | -1.59 [-2.77, -0.42] |
| 5 Proportion of patients without resolution of abscess size | 2 | 70 | Risk Ratio (M-H, Fixed, 95% CI) | 0.90 [0.62, 1.32] |
| 6 Proportion of patients without resolution of abdominal tenderness | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 7 Days to resolution of abdominal tenderness | 2 | 81 | Mean Difference (IV, Random, 95% CI) | -1.70 [-2.86, -0.54] |
| 8 Duration of hospitalisation | 3 | 92 | Mean Difference (IV, Fixed, 95% CI) | -1.31 [-2.05, -0.57] |
| 9 Proportion of non-responders | 2 | 110 | Odds Ratio (M-H, Fixed, 95% CI) | 0.54 [0.25, 1.19] |

### Analysis 1.1. Comparison 1 Needle aspiration and metronidazole versus metronidazole alone, Outcome 1 Proportion of patients remaining febrile.

Review: Image-guided percutaneous procedure plus metronidazole versus metronidazole alone for uncomplicated amoebic liver abscess

Comparison: 1 Needle aspiration and metronidazole versus metronidazole alone

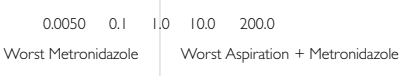
Outcome: 1 Proportion of patients remaining febrile

| Study or subgroup | Aspiration + Metronidazole n/N | Metronidazole n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Sharma 1989 | 1/17 | 3/20 | | 32.0 % | 0.39 [ 0.04, 3.43 ] |
| Van Allan 1992 | 4/20 | 6/21 | | 68.0 % | 0.70 [ 0.23, 2.12 ] |
| **Total (95% CI)** | **37** | **41** | | **100.0 %** | **0.60 [ 0.22, 1.61 ]** |

Total events: 5 (Aspiration + Metronidazole), 9 (Metronidazole)

Heterogeneity: $Chi^2$ = 0.22, df = 1 (P = 0.64); $I^2$ =0.0%

Test for overall effect: Z = 1.01 (P = 0.31)

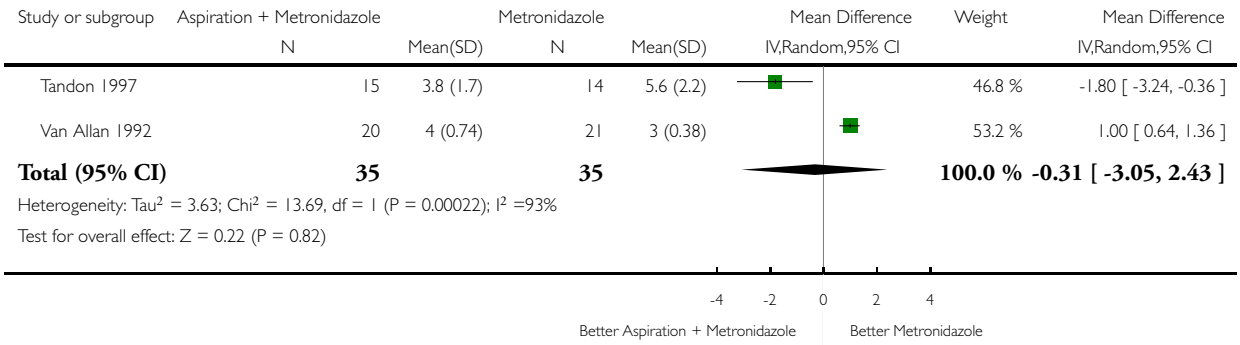


### Analysis 1.2. Comparison 1 Needle aspiration and metronidazole versus metronidazole alone, Outcome 2 Days to resolution of fever.

Review: Image-guided percutaneous procedure plus metronidazole versus metronidazole alone for uncomplicated amoebic liver abscess

Comparison: 1 Needle aspiration and metronidazole versus metronidazole alone

Outcome: 2 Days to resolution of fever

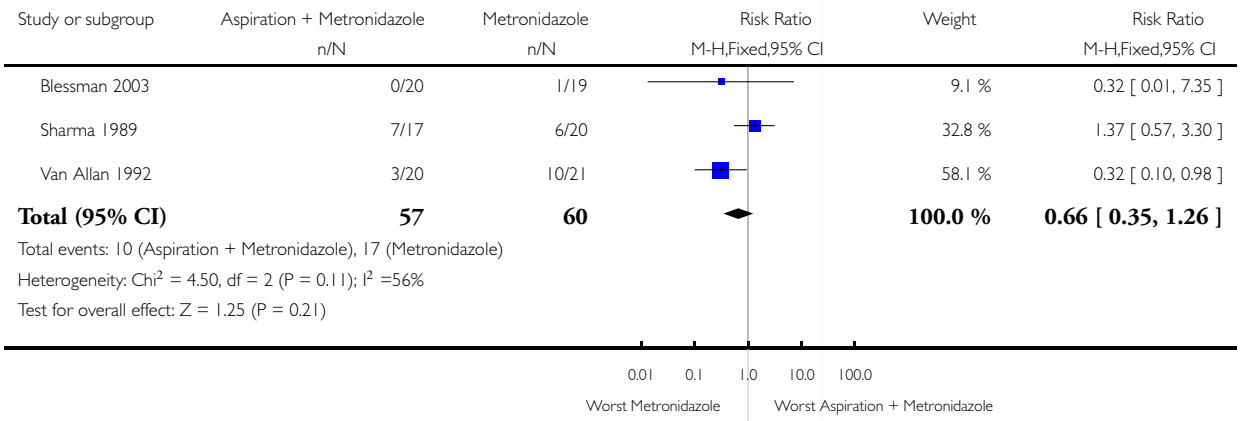



### Analysis 1.3. Comparison 1 Needle aspiration and metronidazole versus metronidazole alone, Outcome 3 Proportion of patients without resolution of pain.

Review: Image-guided percutaneous procedure plus metronidazole versus metronidazole alone for uncomplicated amoebic liver abscess

Comparison: 1 Needle aspiration and metronidazole versus metronidazole alone

Outcome: 3 Proportion of patients without resolution of pain

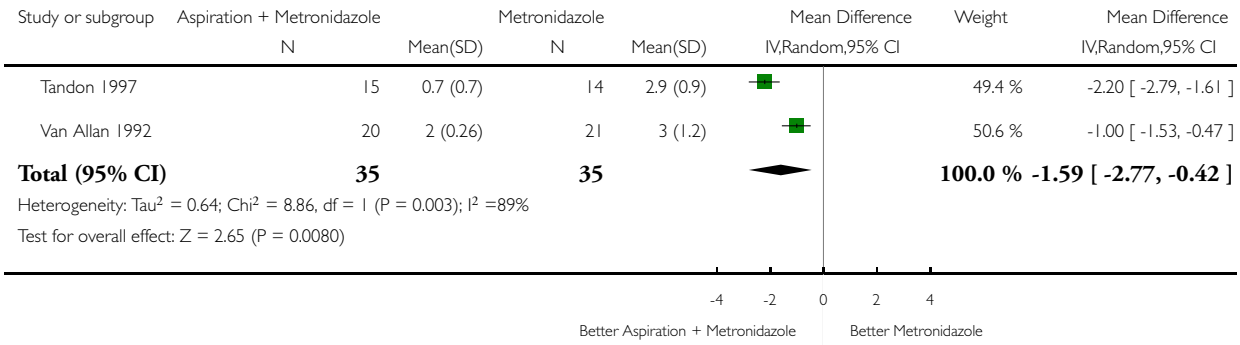


### Analysis 1.4. Comparison 1 Needle aspiration and metronidazole versus metronidazole alone, Outcome 4 Days to resolution of pain.

Review: Image-guided percutaneous procedure plus metronidazole versus metronidazole alone for uncomplicated amoebic liver abscess

Comparison: 1 Needle aspiration and metronidazole versus metronidazole alone

Outcome: 4 Days to resolution of pain

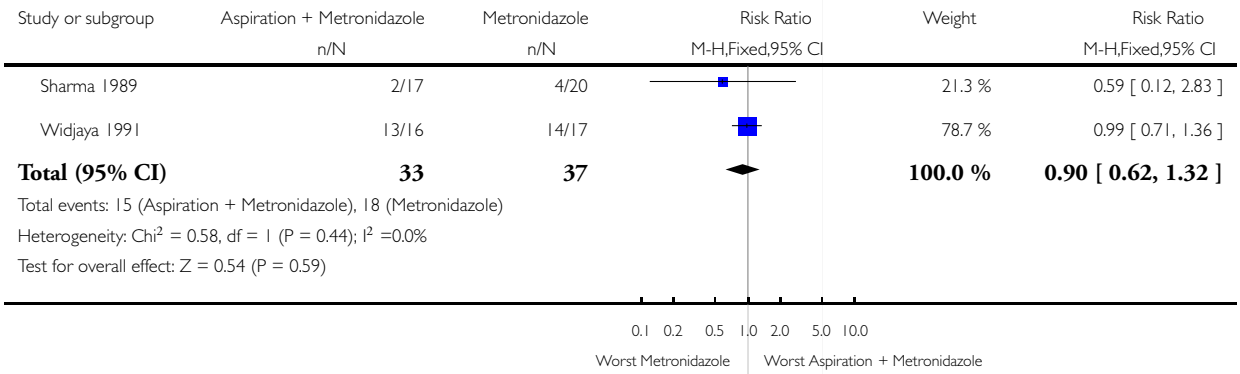



### Analysis 1.5. Comparison 1 Needle aspiration and metronidazole versus metronidazole alone, Outcome 5 Proportion of patients without resolution of abscess size.

Review: Image-guided percutaneous procedure plus metronidazole versus metronidazole alone for uncomplicated amoebic liver abscess

Comparison: 1 Needle aspiration and metronidazole versus metronidazole alone

Outcome: 5 Proportion of patients without resolution of abscess size



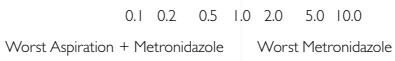
### Analysis 1.6. Comparison 1 Needle aspiration and metronidazole versus metronidazole alone, Outcome 6 Proportion of patients without resolution of abdominal tenderness.

Review: Image-guided percutaneous procedure plus metronidazole versus metronidazole alone for uncomplicated amoebic liver abscess

Comparison: 1 Needle aspiration and metronidazole versus metronidazole alone

Outcome: 6 Proportion of patients without resolution of abdominal tenderness

| Study or subgroup | Aspiration + Metronidazole n/N | Metronidazole n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Blessman 2003 | 4/20 | 7/19 | | 0.0 % | 0.54 [ 0.19, 1.56 ] |
| **Subtotal (95% CI)** | **0** | **0** | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Total events: 4 (Aspiration + Metronidazole), 7 (Metronidazole) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.0 (P < 0.00001) | | | | | |




### Analysis 1.7. Comparison 1 Needle aspiration and metronidazole versus metronidazole alone, Outcome 7 Days to resolution of abdominal tenderness.

Review: Image-guided percutaneous procedure plus metronidazole versus metronidazole alone for uncomplicated amoebic liver abscess

Comparison: 1 Needle aspiration and metronidazole versus metronidazole alone

Outcome: 7 Days to resolution of abdominal tenderness

| Study or subgroup | Aspiration + Metronidazole N | Mean(SD) | Metronidazole N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| de la Rey Nel 1989 | 24 | 4.5 (2.2) | 28 | 6.9 (2.3) | | 41.5 % | -2.40 [ -3.62, -1.18 ] |
| Tandon 1997 | 15 | 1.7 (0.8) | 14 | 2.9 (1.2) | | 58.5 % | -1.20 [ -1.95, -0.45 ] |
| **Total (95% CI)** | **39** | | **42** | | | **100.0 %** | **-1.70 [ -2.86, -0.54 ]** |
| Heterogeneity: Tau² = 0.45; Chi² = 2.69, df = 1 (P = 0.10); I² =63% | | | | | | | |
| Test for overall effect: Z = 2.87 (P = 0.0041) | | | | | | | |

## Analysis 1.8. Comparison 1 Needle aspiration and metronidazole versus metronidazole alone, Outcome 8 Duration of hospitalisation.

Review: Image-guided percutaneous procedure plus metronidazole versus metronidazole alone for uncomplicated amoebic liver abscess

Comparison: 1 Needle aspiration and metronidazole versus metronidazole alone

Outcome: 8 Duration of hospitalisation

| Study or subgroup | Aspiration + Metronidazole N | Mean(SD) | Metronidazole N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Arredondo 1993 | 11 | 4 (0.6) | 11 | 7.2 (3.5) | | 12.4 % | -3.20 [ -5.30, -1.10 ] |
| Tandon 1997 | 15 | 5.8 (0.8) | 14 | 7.4 (1.5) | | 70.0 % | -1.60 [ -2.48, -0.72 ] |
| Van Allan 1992 | 20 | 6.2 (3.46) | 21 | 5 (2.1) | | 17.6 % | 1.20 [ -0.56, 2.96 ] |
| **Total (95% CI)** | **46** | | **46** | | | **100.0 %** | **-1.31 [ -2.05, -0.57 ]** |

Heterogeneity: Chi² = 11.32, df = 2 (P = 0.003); I² =82%

Test for overall effect: Z = 3.46 (P = 0.00054)


## Analysis 1.9. Comparison 1 Needle aspiration and metronidazole versus metronidazole alone, Outcome 9 Proportion of non-responders.

Review: Image-guided percutaneous procedure plus metronidazole versus metronidazole alone for uncomplicated amoebic liver abscess

Comparison: 1 Needle aspiration and metronidazole versus metronidazole alone

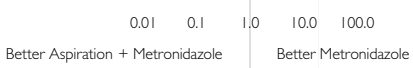
Outcome: 9 Proportion of non-responders

| Study or subgroup | Aspiration + Metronidazole n/N | Metronidazole n/N | Odds Ratio M-H,Fixed,95% CI | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Arredondo 1993 | 0/15 | 8/15 | | 47.8 % | 0.03 [ 0.00, 0.56 ] |
| de la Rey Nel 1989 | 13/37 | 15/43 | | 52.2 % | 1.01 [ 0.40, 2.54 ] |
| **Total (95% CI)** | **52** | **58** | | **100.0 %** | **0.54 [ 0.25, 1.19 ]** |

Total events: 13 (Aspiration + Metronidazole), 23 (Metronidazole)

Heterogeneity: Chi² = 5.51, df = 1 (P = 0.02); I² =82%

Test for overall effect: Z = 1.53 (P = 0.13)



# APPENDICES

## Appendix 1. Search strategies

| Database | Time of search | Searched Items |
|---|---|---|
| The Cochrane Hepato-Biliary Group Controlled Trials Register | September 2007. | (metronidazole OR 'image-guided percutaneous' OR (needle AND (aspiration OR biops*)) OR 'catheter-drain*') and (amoeb* OR ameb*AND (liver OR hepatic) AND abscess*) |
| Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library | Issue 2, 2007. | #1 MeSH descriptor Metronidazole explode all trees in MeSH products<br>#2 MeSH descriptor Biopsy, Needle explode all trees in MeSH products<br>#3 MeSH descriptor Drainage explode all trees in MeSH products<br>#4 metronidazole OR image-guided percutaneous OR needle aspiration OR catheter drain* in All Fields in all products<br>#5 (#1 OR #2 OR #3 OR #4)<br>#6 MeSH descriptor Liver Abscess, Amebic explode all trees in MeSH products<br>#7 am*eb* AND (liver OR hepatic) AND abscess* in All Fields in all products<br>#8 (#6 OR #7)<br>#9 (#5 AND #8) |
| MEDLINE | 1950 to October 2007. | #1 explode "Metronidazole"/ all subheadings<br>#2 explode "Biopsy-Needle"/ all subheadings<br>#3 explode "Drainage"/ all subheadings<br>#4 metronidazole or image-guided percutaneous or needle aspiration or catheter drain*<br>#5 #1 or #2 or #3 or #4<br>#6 explode "Liver-Abscess-Amebic"/ all subheadings<br>#7 am*eb* and (liver or hepatic) and abscess*<br>#8 #6 or #7<br>#9 #5 and #8<br>#10 am*eb* AND (liver OR hepatic) AND abscess*<br>#11 #9 and #10 |
| EMBASE | 1980 to October 2007. | #1 explode "metronidazole"/ all subheadings<br>#2 explode "needle-biopsy"/ all subheadings<br>#3 explode "percutaneous-drainage"/ all subheadings<br>#4 metronidazole or image-guided percutaneous or needle aspiration or catheter drain*<br>#5 #1 or #2 or #3 or #4<br>#6 explode "liver-amebiasis"/ all subheadings<br>#7 am*eb* and (liver or hepatic) and abscess* |

(*Continued*)

| | | |
|---|---|---|
| | | #8 #6 or #7<br>#9 #5 and #8<br>#10 random* or blind* or placebo* or meta-analysis<br>#11 #9 and #10 |
| Science Citation Index Expanded (http://portal.isiknowledge.com/portal.cgi?I | 1945 to October 2007. | #1 TS=(metronidazole OR image-guided percutaneous OR needle aspiration OR catheter drain*)<br>#2 TS=(am*eb* AND (liver OR hepatic) AND abscess*)<br>#3 #2 AND #1<br>#4 TS=(random* or blind* or placebo* or meta-analysis)<br>#5 5 #4 AND #3 |

## WHAT'S NEW

Last assessed as up-to-date: 4 April 2008.

| | | |
|---|---|---|
| 10 April 2008 | Amended | Converted to new review format. |

## HISTORY

Protocol first published: Issue 3, 2004

Review first published: Issue 1, 2009

## CONTRIBUTIONS OF AUTHORS

Norberto C Chavez-Tapia. Co-ordinating, data collection, designing search strategies, undertaking searches, screening search results, screening retrieved papers against eligibility criteria, extracting data from papers, writing to authors of papers for additional information, data management for the review, entering data into RevMan, analysis of data, writing the review.

Jorge Hernandez-Calleros. Data collection, undertaking searches, screening search results, screening retrieved papers against eligibility criteria, extracting data from papers.

Felix I Tellez-Avila. Data collection, designing search strategies, undertaking searches, screening search results, screening retrieved papers against eligibility criteria, extracting data from papers, analysis of data, writing the review.

Aldo Torre-Delgadillo. Interpretation of data, providing a clinical perspective, and providing general advice on the review.

Misael Uribe. Performing previous work that was the foundation of the current review, providing general advice, and securing funding for the review.

## DECLARATIONS OF INTEREST

None known.

## SOURCES OF SUPPORT

### Internal sources

- None, Not specified.

### External sources

- None, Not specified.

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol of this review was published with a title 'Metronidazole with or without image-guided percutaneous procedure for uncomplicated amoebic liver abscess'. We have modified it into 'Image-guided percutaneous procedure plus metronidazole *versus* metronidazole alone for uncomplicated amoebic liver abscess' for clearer wording.

In the excluded studies, left lobe abscesses was also considered as an exclusion criteria.

The Science Citation Index Expanded was included in the searching for identification methods.

Data analysis was performed with Review Manager Version 5.0 instead of Review Manager Version 4.2.

## NOTES

Additional information was requested to all authors by e-mail or conventional mail.

En este meta-análisis evaluamos el papel de la aspiración percutánea guiada por imagen adicionada al uso de metronidazol en pacientes con abscesos hepáticos amibianos. El motivo de realizar el estudio fue la alta tasa de pacientes infectados en el mundo (40 millones) y el alto número de muertes asociadas (40,000-110,000) principalmente en los países en vías de desarrollo.

Encontramos, que a pesar de que cuando se cuenta con el recurso, la punción guiada por imagen de los abscesos hepáticos amibianos goza de gran popularidad su efecto no parece ser tan importante como tradicionalmente se piensa. Pocos estudios y de poca calidad avalan su uso.

**Referencias a este artículo: 10**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RIC

ARTÍCULO ORIGINAL

# Endoscopic treatment of high-risk bleeding ulcers: success, rebleeding and mortality

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## ABSTRACT

**Introduction and aims.** Endoscopic treatment of peptic ulcers with high-risk stigmata has been probed. The rates of recurrent bleeding, need for emergent surgery and death are related to Forrest Classification, Blatchford's modified risk score and the kind of endoscopic treatment used (monotherapy *vs.* dual). The aims of the present study were to report the success of endoscopic therapy in the reduction of the rate of initial success, recurrent bleeding, the need for surgery, and the mortality rate for patients with bleeding peptic ulcer and high-risk stigmata. **Patients and methods.** From a retrospective view, patients seen from September 2004 to March 2007 who had peptic ulcers Forrest Ia, Ib, IIa and/or IIb were included. **Results.** Fifty-six patients were included (mean [SD] age 57.3 ± 16.6 years). The success rate was 91%, whilst the rest of the patients required immediate surgery. Recurrent bleeding was presented in 14 (27%) patients and eight (14.2%) required emergency surgery. The mortality rate was 3.6%. No factors were associated with the risk of failure to initial treatment, recurrent bleeding or need for surgery. The use of monotherapy by endoscopy was associated with the mortality. The variable "fellow alone" was not associated with any kind of outcome. **Conclusion.** Complication rate is similar to previous reports of general hospitals, but is higher than those of referral centers. Endoscopic monotherapy is associated with a major mortality risk.

**Key words.** Peptic ulcer. Endoscopic Hemostasis. Hemorrhage. Treatment Failure. Mortality.

***Tratamiento endoscópico de las úlceras de alto riesgo: éxito, resangrado y mortalidad***

## *RESUMEN*

***Introducción y objetivos.*** *El tratamiento endoscópico ha probado ser eficaz en las úlceras pépticas con estigmas de alto riesgo. Las tasas de recurrencia de sangrado, necesidad de cirugía y muerte están relacionadas con la clasificación de Forrest, el puntaje del Score modificado de Blatchford y el tipo de tratamiento utilizado (único vs. doble). El objetivo del estudio fue reportar los resultados del tratamiento endoscópico (tasa de recurrencia de sangrado, necesidad de cirugía y mortalidad) en nuestro medio.* ***Pacientes y métodos.*** *Se evaluaron de manera retrospectiva los pacientes que acudieron de septiembre 2004 a marzo de 2007. Se incluyeron pacientes con úlceras clasificadas como de alto riesgo (Forrest Ia, Ib, IIa, IIb).* ***Resultados.*** *56 pacientes fueron incluidos (27 mujeres y 29 hombres; edad media (DE) 57.3 ± 16.6 años). El control en la primera sesión se logró en 91% de los pacientes, el resto de pacientes requirieron de cirugía inmediata. En 14 pacientes (27%) se documentó recurrencia de sangrado y ocho (14.2%) pacientes requirieron tratamiento quirúrgico urgente. La mortalidad en el grupo fue de 3.6%. No se identificaron factores asociados al éxito inicial, recurrencia de sangrado o necesidad de cirugía urgente. La aplicación de monoterapia endoscópica está asociada con el desenlace de mortalidad. No se encontró asociación de alguno de los desenlaces evaluados y los procedimientos realizados por médicos residentes.* ***Conclusión.*** *La tasa de complicaciones en nuestro instituto es similar a lo reportado por otros centros de atención general de países de primer mundo; sin embargo es más alta que la reportada por centros de referencia. El uso de monoterapia endoscópica se asocia a una mayor mortalidad.*

***Palabras clave.*** *Úlcera péptica. Hemostasia endoscópica. Hemorragia. Falla al tratamiento. Mortalidad.*

## INTRODUCTION

There is no doubt that endoscopic treatment of peptic ulcer hemorrhage is superior to conservative treatment, with a significant reduction in recurrent bleeding, emergency surgery and death.[1,2] Endoscopic methods for hemostasis include injection therapy, thermal coagulation, and mechanical therapy with hemoclips and bands. The success rate expected with endoscopic therapy (ET) is 95%.[3] The frequency of recurrent bleeding in referral centers has been reported in less than 15% of patients.[4] Previous studies have shown that dual ET (DET) is better than epinephrine injection alone, but not different from any other single ET (thermal or mechanical).[5] However, epinephrine injection is still among the most popular ET because of its safety, low cost, and it is application easiness.

The aim of this study was to report the experience of ET in the initial success, rate of recurrent bleeding, the need for surgery, and death rate in patients with bleeding peptic ulcer and/or high-risk stigmata for recurrent bleeding. The second aim was to determine the frequency of each treatment modality (DET *vs.* monotherapy).

## PATIENTS AND METHODS

We retrospectively reviewed the electronic and paper-based records of patients with high-risk bleeding ulcers (HRBU) whom underwent an endoscopy at the Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán" from September 2004 to March 2007. For this study, HRBU was defined as patients with hemorrhage from peptic ulcer disease (gastric or duodenal) with major bleeding stigmata, defined by groups according to Forrest's classification:[6] Ia (spurting hemorrhage), Ib (oozing hemorrhage), IIa (nonbleeding visible vessel), and IIb (adherent clot). Monotherapy was defined as epinephrine injection alone on a 1:10 000 dilution. Dual therapy was considered when, besides epinephrine injection, an extra ET method was used (heat probe, argon-plasma coagulation, hemoclips). Patients with haematemesis and those who were haemodynamically unstable underwent an endoscopy after initial resuscitation. In all patients, according to institutional politics, informed consent was obtained before the procedure. A regular diagnostic endoscope was initially used (GIF-100, GIF-130, GIF-140 or GIF-160, Olympus, Japan) and therapeutic modality (monotherapy or dual) was assigned according with physician criteria. Aside from epinephrine injection, ET was performed with heat probe coagulation, Argon plasma coagulation or Hemoclips (Olympus, Japan). All conscious patients were sedated with midazolam, phentanyl and/or propofol.

### Initial endoscopic haemostasis

In Forrest Ia and Ib ulcers, initial success was accomplished when endoscopic haemostasis was reached within the procedure. In Forrest IIa and IIb ulcers, initial success was accomplished when ET was applied without immediate bleeding.

### Recurrent bleeding

Recurrent bleeding was clinically defined as the passage of haematemesis or melena, or both, coupled with the development of shock or decrease in hemoglobin concentration by at least 2 g/dL after initial stabilization of 24 hours or aspiration of fresh blood from nasogastric tube.[3,5] Bleeding was confirmed by endoscopy or surgery in all cases.

The Forrest's classification, clinical, laboratory, and demographic characteristics were recorded, modified Blatchford Score Risk, the initial endoscopic technique for haemostasis, rebleeding, requirement for surgery, blood transfusion, and mortality during the first 30 days after the procedure.

### Statistical Analysis

Results are expressed as means and ± SD. Comparison of quantitative data were performed using the Student's t-test or Mann-Whitney U test, according with variable distribution. The differences between proportions of categoric data were obtained by the Fisher exact test when the number of expected subjects was less than 5, and by the Chi-square test otherwise. A P-value $< 0.05$ was considered statistically significant. All statistical analyses were conducted using the statistics program SPSS/PC version12.0 (Chicago, IL, USA).

## RESULTS

During the study period, 56 patients with upper gastrointestinal bleeding due to peptic ulcer were admitted to our hospital. Twenty-seven women (48.2%) and twenty-nine men (51.8%) were included, with a mean age of 57.3 ± 16.6 years. Clinical, demographic and laboratory characteristics are shown in table 1. Duodenum was the most common localization, and Forrest IIb was the most frequent grade

(Figure 1). A total of 31 (55.3%) patients received proton pump inhibitors (PPI) before the event; 25 (44.6%) patients had previous peptic ulcer disease (according to paper based records); and 14 (25%) patients were positive to histological examination for *H. pylori* infection. The mean number of endoscopic procedures by patient was 2 (range 1-4). Twenty-four (42.9%) patients received single ET and thirty-two (57.1%) patients underwent dual therapy (Figure 2). Mean epinephrine volume injected was 15 ± 6.6 milliliters.

Initial success for endoscopic haemostasis was achieved in 51 patients (91%). Primary haemostasis was not possible in five (9%) patients whom went directly to surgery. Two of them subsequently died (between five and twenty days after surgery). Recurrent bleeding was documented in 14/51 (27.4%) patients, with a median time to bleeding recurrence of 5 (range 1-30) days. Beside the five patients that required surgery due to failure to initial success; three patients underwent emergency surgery of recurrent bleeding. During 30 days of follow up, mortality was 19.6% (11 patients), although only in two patients was the cause of death directly related to ulcer bleeding (3.6%). No statistical differences between patients with and without any endpoint were found (Table 2).

No differences were found according to different types of endoscopic treatment. Table 3 displays the outcomes, frequency of monotherapy and procedures by fellows. No ET (mechanical or thermal) beside epinephrine was used as monotherapy.

**Table 1.** Clinical and demographic characteristics of patients (n = 56).

| Variable | n (%) |
|---|---|
| Age, *y** | 57.3 ± 16.6 |
| Female | 27 (48.2) |
| Hemoglobin, *g/dL** | 9.5 ± 2.5 |
| INR*, † | 1.3 ± 0.7 |
| NSAID‡, *yes* | 15 (26.8) |
| Antiplatelet agents, *yes* | 12 (21.4) |
| Oral anticoagulation, *yes* | 7 (12.5) |
| Endoscopic treatment, *single* | 24 (42.9) |
| Shock, *yes* | 12 (21.4) |
| Comorbilities | |
| Hypertension | 19 (34) |
| Diabetes mellitus | 17 (30.3) |
| CKD§ | 9 (16) |
| Cancer | 9 (16) |
| Cirrhosis | 6 (10.7) |
| Stroke(history) | 5 (8.9) |
| Autoimmune disease | 5 (8.9) |
| Heart disease | 3 (5.3) |

* Expressed in mean (SD). † International Normalized Ratio. ‡ Non-Steroid anti-inflammatory drugs. § Chronic kidney disease.

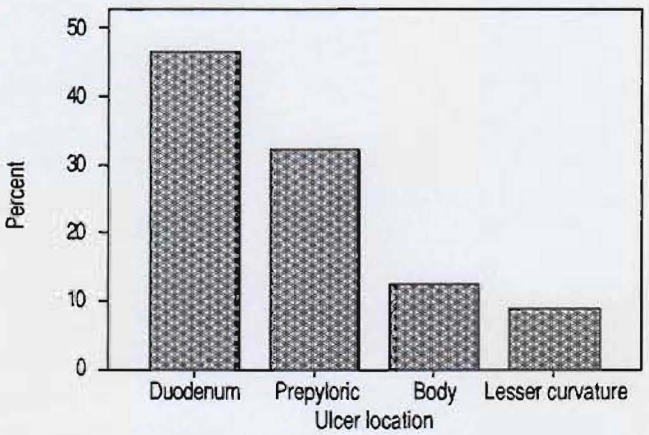


*Figure 1. Frequencies of ulcer location.*

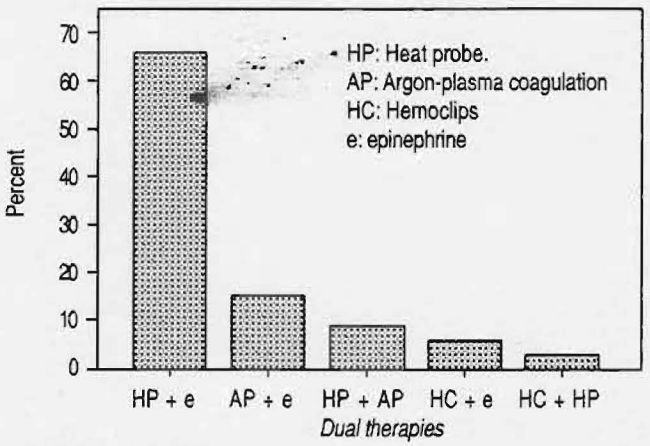


*Figure 2. Dual therapies.*

## DISCUSSION

This report represents the first data regarding endoscopic therapy and HRBU from our center and, to the best of our knowledge, from any other Mexican or Latin American center. This is an important worldwide topic and information from other Latin American centers will be useful to improve the quality and increase survival in these kinds of patients. Our results are similar to some reports on recurrent bleeding, emergency surgery, and mortality rates,[5] but are still slightly higher in respect to other foreign referral centers.[4] Increased complication rates could be explained by the higher punctuation of severity in Blatchford's modified Risk Score[7] present in our patients (82.1% have 2 or more points); since monotherapy, ulcer location, sub-groups of Forrest's classification, symptoms,

of *H. pylori* on a high risk population such as Mexican one.

Nowadays, dual therapy in endoscopy is the most accepted treatment due to HRBU. This modality has shown to be better when compared to epinephrine injection alone for reducing further bleeding, the need for emergency surgery and mortality.[5,8-10] According to our results, there was no correlation between recurrent hemorrhage and need for emergency surgery with the use of monotherapy *vs.* dual ET. We consider that this finding is due to the reduced sample number and do not reflect the best feasible results with single ET, compared to other worldwide centers (same phenomena with Forrest classification). Mortality in our population was in agreement with other previous reports.

The numbers of procedures carried out by fellows alone were few, and this small number limits comparison on this feature. However, according to these results, it seems likely that there are no implications if the procedure is performed solely by a fellow. No differences with the endpoint (rate of initial success, recurrent bleeding, the need for surgery, and death rate) were found.

Regarding *H. pylori* infection, compared with previous reports in Mexican population,[11] the prevalence in our group of patients was low. A possible explanation for this finding is that the diagnostic methods used were different. In a work made by Torres, *et al.*[11] the diagnostic tool used for *H. pylori* infection was a serologic testing using ELISA method for detection of IgG antibodies. Another important factor is that in only 30 of our patients a tissue sample for *H. pylori* evaluation was obtained; so the prevalence considering this fact is higher (14/30; 46.6%), and is consistent with previous reports.[11,12] Another possible explanation is the previous administration of *H. pylori* eradication treatment; unfortunately this information was not available.

Limitations of our work are the sample number and the retrolective collection of data. However, this is the only information available as to evaluate therapeutic issues in upper non-variceal gastrointestinal bleeding. Future prospective studies are necessary to confirm these results.

In conclusion, the rates of complications in our institute are higher than in other referral centers. The use of epinephrine injection alone, age, symptom of presentation or the procedure made by a fellow alone are not related factors of initial success, recurrent bleeding, or need of emergency surgery. Our results suggest that mortality rate may be influenced by the use of dual ET.

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Este trabajo representa los primeros datos procedentes del Departamento de Endoscopia del Instituto Nacional de la Nutrición Salvador Zubirán en relación con el tratamiento endoscópico de los pacientes con úlceras pépticas sangrantes. Encontramos que nuestros resultados, aunque buenos, aun eran perfectibles debido a que nos encontrábamos en los rangos de eficacia similares a los reportados por hospitales generales de primer mundo. La principal causa de dichos resultados, pudimos entender que se relacionaban con el uso de monoterapia endoscópica. Posterior a este trabajo, modificamos nuestra conducta y actualmente el tratamiento utilizado en nuestro departamento es la terapia endoscópica dual.

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*RAPID COMMUNICATION*

# Prevalence of metabolic syndrome, obesity and diabetes type 2 in cryptogenic cirrhosis

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## Abstract

**AIM:** To evaluate the prevalence of metabolic syndrome (MS), obesity and type 2 diabetes mellitus (T2DM) in a group of Mexican Mestizo patients with cryptogenic cirrhosis (CC) and to compare this group with patients with cirrhosis secondary to other causes (disease controls).

**METHODS:** Patients with CC, diagnosed between January, 1990 and April, 2005, were included in a retrospective study. Patients with cirrhosis caused by chronic hepatitis C, alcohol abuse or autoimmune hepatitis (AIH) served as disease controls.

**RESULTS:** A total of 134 patients with CC were analyzed. Disease controls consisted of 81 patients with chronic hepatitis C, 33 with alcohol abuse and 20 with AIH. The median age of patients with CC was 57 years (range, 16-87); 83 (61.9%) patients were female; 53 (39.6%) were Child A, 65 (48.5%) Child B, and 16 (11.9%) were Child C cirrhosis. The prevalence of MS (29.1% *vs* 6%; $P < 0.001$), obesity (16.4% *vs* 8.2%; $P = 0.04$) and T2DM (40% *vs* 22.4%; $P = 0.013$) was higher in CC patients than in disease controls. There were no differences in sex, age or liver function tests between the two groups.

**CONCLUSION:** The prevalence of MS, obesity and T2DM were higher in patients with CC than in patients with cirrhosis secondary to others causes. Our findings support the hypothesis that non-alcoholic steatohepatitis (NASH) plays an under-recognized role in CC.



**Key words:** Cryptogenic chronic hepatitis; Metabolic syndrome; Obesity; Diabetes mellitus

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## INTRODUCTION

The diagnosis of "cryptogenic" cirrhosis is made after an extensive evaluation has excluded recognizable etiologies[1]. The prevalence of cryptogenic cirrhosis (CC) ranges from 5% to 30% in cirrhotic patients[1]. In Mexico, the etiology of cirrhosis remains unclear in 10% patients despite an extensive evaluation[2]. Several etiological possibilities are offered in such patients. These include occult alcohol abuse, silent autoimmune hepatitis (AIH), occult viral (non-B, non-C) hepatitis, and progression of nonalcoholic steatohepatitis (NASH)[3].

The prevalence of clinically silent autoimmune hepatitis in patients with CC is unknown; however, several studies have suggested that a significant number of patients with CC may have burnt-out AIH[4-6]. Occult virus disease (Non-B, non-C hepatitis) is considered to account for about 15% of post-transfusion hepatitis[7] and may exist in a silent form for several years[8]. Obesity and non-insulin dependent diabetes mellitus are the

two most common conditions associated with NASH[9], which is frequently asymptomatic[10] and can progress silently to cirrhosis with definitive histological features[10].

The aim of the present study was to characterize the metabolic disturbances [prevalence of metabolic syndrome (MS), obesity and type 2 diabetes mellitus (T2DM)] in a group of Mexican Mestizo patients with CC. In particular, we compared the prevalence of metabolic disturbances in the cryptogenic group with patients with cirrhosis due to other causes: hepatitis C without prior alcoholism, alcohol abuse and AIH.

## MATERIALS AND METHODS

In a retrospective manner, we examined the medical records (paper and electronic-based records) of all patients with CC diagnosed from January, 1990 to April, 2005. We also included in a random fashion, disease controls consisting of patients with cirrhosis caused by chronic hepatitis C, alcohol abuse and AIH.

Diagnosis of CC was made after an exhaustive evaluation failed to provide a specific etiology. The data collected included the hepatologic diagnosis, co-morbid conditions, complications of portal hypertension if present, and major forms of treatment. Additional information was obtained from clinical charts, hospital records, the clinic and hospital laboratory databases, and by personal or telephone interview. Patients were included in the study if sufficient data was available and if the diagnosis was confirmed on review of all the available information.

The diagnosis of cirrhosis was made on the basis of clinical, laboratory and imaging data. In addition, histological findings were available in 56 (42%) CC patients. Biopsy was not performed in 78 patients, either because of refusal by the patient or their in-charge physician. Data collected included gender, age at diagnosis of cirrhosis, presenting symptoms, potential occupational exposure to hepatotoxins, family history of liver disease, and family or personal history of autoimmune diseases. Risk assessment for viral hepatitis included history of exposure to intravenous drugs, blood transfusions, tattoos, other known percutaneous needle exposures, and high-risk sexual behavior. All patients underwent extensive serological testing including hepatitis B and C screening [hepatitis B surface antibody, surface antigen, and anticore antibody, and hepatitis C enzyme-linked immunosorbent assay (Abbott Laboratories, Abbott Park, IL)], iron studies (ferritin, iron, iron binding capacity, and tissue assessment if the diagnosis was questionable), ceruloplasmin, antinuclear antibody (ANA), antimitochondrial antibody, and $\alpha$1-antitrypsin. Quantitative immunoglobulin levels (IgG, IgM, IgA) were obtained in all patients. Assessment of $\alpha$1-antitrypsin level was performed using isoelectric focusing (pH range, 4.0-5.0).

Patients with CC who had a positive antinuclear antibody (positive > 1:80) test, an index of autoimmune hepatitis, were evaluated by the International Autoimmune Hepatitis (IAH) score, based on clinical and laboratory parameters as previously described[11]. None of the patients received steroid therapy, and thus the IAH score was calculated using the Minimal Required Parameters, wherein a score of 10 to 15 is suggestive of autoimmune hepatitis, and a score of greater than 15 is considered definitive. The term overweight was defined as body mass index (BMI) greater than 25, while obesity was defined as a BMI greater than 30. BMI was calculated by dividing the patients' body weight by the square of their height expressed as $kg/m^2$. BMI was calculated using the average adult weight reported by the patient and the patient's height. In all cases, type 2 DM was diagnosed by the presence of recurrent fasting hyperglycemia ($\geq$ 126 mg/dL), requiring treatment with dietary management, oral hypoglycemic agents, or insulin therapy. Dyslipidaemia was considered in the presence of high serum triglycerides (> 150 mg/dL) and/or low high-density lipoproteins (< 50 mg/dL in women and < 40 mg/dL in men). The diagnosis of MS was made according to the NCEP (ATP) Ⅲ consensus[12,13].

The absolute and relative frequencies were used for summary. The data is presented as mean ± SD. The one-way ANOVA test or Kruskal-Wallis was used to compare parametric or nonparametric variables, respectively. The $\chi^2$ test was used for categorical variables. A $P$ value ($\alpha$) of < 0.05 was considered significant. Bonferroni correction for $P$-value was applied for multiple comparisons, calculated as $\alpha/n$. For multiple comparisons a $P$ value of < 0.016 was considered significant. All statistical analyses were conducted using the statistics program SPSS/PC version 12.0 (Chicago, IL, USA).

## RESULTS

After careful review of the medical records, 50 patients who were originally classified as CC in the hospital registry were found to have other causes of liver disease. The main reason for this discrepancy was incomplete investigation or erroneous interpretation of the test results when the patients were referred to our center. These patients were initially listed as CC, but the diagnosis was not corrected in the registry when the new information became available. Other less common reasons for patient exclusion were incomplete medical information and indeterminate test results. For the final analysis, a total of 134 patients with CC were included in the study. In addition, EIGHTY ONE patients with chronic hepatitis C, thirty-three with alcohol abuse and twenty with AIH were evaluated as disease controls. The demographic, clinical, and laboratory characteristics of the study subjects are summarized in Table 1. In patients with CC, the median age was 57 years (range 16-87); 83 (61.9%) were female; and 53 (39.6%) had Child A cirrhosis, 65 (48.5%) were Child B and 16 (11.9%) were Child C.

Five patients were determined to have moderate alcohol consumption (< 2 drinks/d), but this was not considered to be the cause of their liver disease, either by the hepatologist or their primary care physician. None of the patients had a history of intravenous drug

**Table 1 Demographic, clinical and laboratory parameters of patients with cryptogenic cirrhosis and non-cryptogenic cirrhosis**

| Variable | Cryptogenic (*n* = 134, %) | Non-cryptogenic (*n* = 134, %) | *P* |
|---|---|---|---|
| Sex (female) | 83 (62) | 75 (56) | 0.32 |
| DM | 53 (40) | 30 (22.4) | 0.013 |
| HBP | 24 (18) | 14 (10.4) | 0.08 |
| Hyperuricemia | 13 (10) | 2 (1.5) | 0.003 |
| Dyslipidaemia | 72 (54) | 8 (6) | < 0.001 |
| Overweight (BMI > 25) | 103 (77) | 106 (79) | 0.65 |
| Obesity (BMI > 30) | 22 (16.4) | 11 (8.2) | 0.04 |
| MS | 39 (29.1) | 8 (6) | < 0.001 |
| Age (yr, mean ± SD) | 54.6 ± 14.3 | 56.8 ± 11.4 | 0.15 |
| BMI (mean ± SD) | 27 ± 4.6 | 26 ± 4 | 0.22 |
| ALT (U/L, mean ± SD) | 52.5 ± 59 | 57.5 ± 33 | 0.72 |
| AST (U/L, mean ± SD) | 67.1 ± 60 | 77.8 ± 46 | 0.19 |

DM: Diabetes mellitus; HBP: High blood pressure; BMI: Body mass index (calculated as patient's body weight divided by the square of the height expressed in kg/m$^2$); MS: Metabolic syndrome.

**Table 2 Comparison of patients with cryptogenic cirrhosis with and without liver tissue examination**

| Variable | Liver biopsy (*n* = 56, %) | No liver biopsy (*n* = 78, %) | *P* |
|---|---|---|---|
| Sex (female) | 37 (66) | 46 (59) | 0.47 |
| DM | 13 (23) | 40 (51) | 0.001 |
| HBP | 7 (13) | 17 (22) | 0.18 |
| Hyperuricemia | 3 (5) | 10 (13) | 0.03 |
| Dyslipidaemia | 21 (38) | 51 (65) | 0.002 |
| Overweight (BMI > 25) | 46 (82) | 57 (73) | 0.29 |
| Obesity (BMI > 30) | 4 (7) | 18 (23) | 0.017 |
| MS | 10 (18) | 29 (37) | 0.02 |
| Child-Pugh A | 29 (52) | 24 (31) | 0.02 |
| Age (yr, mean ± SD) | 55.8 ± 14.5 | 53.7 ± 14 | 0.42 |
| BMI (mean ± SD) | 26.2 ± 4.6 | 27.3 ± 4.6 | 0.28 |
| ALT (U/L, mean ± SD) | 51.8 ± 38 | 52.9 ± 70 | 0.91 |
| AST (U/L, mean ± SD) | 66 ± 48 | 68 ± 69 | 0.86 |
| Albumin (g/dL, mean ± SD) | 3.3 ± 0.7 | 2.9 ± 0.6 | 0.01 |
| Alkaline Phosphatase (U/L, mean ± SD) | 150 ± 72 | 154 ± 74 | 0.7 |
| Child-Pugh score (mean ± SD) | 6.9 ± 2.7 | 7.7 ± 1.8 | 0.06 |

DM: Diabetes mellitus; HBP: High blood pressure; BMI: Body mass index (calculated as patient's body weight divided by the square of the height expressed in kg/m$^2$); MS: Metabolic syndrome.

use. Seven patients had a history of blood transfusions, but none of them had hepatitis C or hepatitis B virus infections. Seven patients had a positive family history of liver disease. A positive antinuclear antibody test was present in 13 patients (10%), but a definite score for autoimmune hepatitis was not present in any patient. Serum α1-antitrypsin deficiency was assessed in 6 patients. However, none of the patients had biochemical or histological evidence of α1-antitrypsin deficiency. Serum ferritin and iron saturation tests were measured in all patients and were within normal/non-diagnostic limits. Genetic testing for hemochromatosis was not performed, and thus carriage of abnormal alleles cannot be excluded. There was no difference in the liver function tests or the Child Pugh score between patients with CC who had a liver biopsy ($n$ = 56, 42%) and those did not ($n$ = 78, 58%). However, patients without liver tissue examination had higher prevalence of metabolic disturbances (Table 2).

The prevalence of MS, obesity and T2DM were greater in CC patients compared to patients without CC (Table 1). When patients without CC were classified by etiology (hepatitis C, alcohol, and AIH), significant differences in MS prevalence were observed: 6.2% in hepatitis C, 6% in patients with alcohol abuse, and 5% in AIH *vs* 29.1% in CC patients ($P$ < 0.001). The differences in the prevalence of T2DM persisted, but when Bonferroni correction for multiple-comparison was used, only obesity showed a statistical trend (Table 3). The prevalence of the different components of MS were analyzed separately; dyslipidaemia ($P$ < 0.001) and abnormal glucose ($P$ = 0.01) were more common in CC patients than in disease controls, while high blood pressure (HBP) showed a trend towards significance ($P$ = 0.08). Hyperuricemia was more frequent in CC patients (10% *vs* 1.5%, $P$ = 0.003).

## DISCUSSION

The present study shows a high prevalence of MS, obesity, and T2DM in Mexican Mestizo population with CC. The relationship between T2DM, obesity, and cirrhosis has been much debated[14-17]. To our knowledge, this is the first study that shows an association between MS and CC. There is less controversy regarding an association between MS, obesity, T2DM, and NASH[18], and several previous studies have shown a relationship between components of MS and NASH as well as the severity of liver fibrosis[19-21]. MS is a worldwide problem with a high prevalence rate[22], and in agreement with our data this abnormality, along with some of its components, is more frequent in CC than in patients with cirrhosis caused by other etiologies. This finding is very important because it provides further evidence to support the theory that NAFLD/NASH can progress to cirrhosis in some patients.

The prevalence of MS was 500% higher in patients with CC compared to patients without CC. When the prevalence of each of the MS components in patients with and without CC was analyzed, only abnormal glucose values and dyslipidaemia showed statistically significant differences between the two groups (Table 1). There was no difference between the two groups with respect to the prevalence of HBP and being overweight. This may be related to the hemodynamic changes and malnutrition, seen commonly in cirrhotic patients. The mean ± SD of HDL and triglyceride levels in CC patients were similar in women (43.4 ± 10.9 mg/dL and 92.4 ± 49 mg/dL) and men (39.5 ± 8.5 mg/dL and 111.3 ± 59 mg/dL). Both of these test values were abnormal when the NCEP guidelines were taken into consideration (abnormal HDL serum levels < 50 mg/dL for women and < 40 mg/dL for men); prevalence of low HDL levels was seen in 76.7% women and 41.5% men. An observation not previously reported is the finding of higher prevalence (statistically significant) of hyperuricemia in CC compared to disease controls. Hyperuricemia is not accepted as

**Table 3 Comparison of patients with cryptogenic cirrhosis and disease controls separated by the etiology of cirrhosis**

| Variable | Cryptogenic (*n* = 134, %) | CHC (*n* = 81, %) | Alcohol (*n* = 33, %) | AIH (*n* = 20, %) | *P* |
|---|---|---|---|---|---|
| Sex (female) | 83 (62) | 54 (66.7) | 7 (21.2) | 14 (70) | < 0.001 |
| DM | 53 (40) | 17 (21) | 10 (30.3) | 3 (15) | 0.013 |
| HBP | 24 (18) | 8 (10) | 4 (12.1) | 2 (10) | 0.36 |
| Hyperuricemia | 13 (10) | 1 (1.2) | 0 (0) | 1 (5) | 0.027 |
| Dyslipidaemia | 72 (54) | 5 (6) | 1 (3) | 2 (10) | < 0.001 |
| Overweight (BMI > 25) | 103 (77) | 63 (78) | 27 (81.8) | 16 (80) | 0.93 |
| Obesity (BMI > 30) | 22 (16.4) | 5 (6.2) | 5 (15.2) | 1 (5) | 0.10 |
| MS | 39 (29.1) | 5 (6.2) | 2 (6) | 1 (5) | < 0.001 |
| Age (yr, mean ± SD) | 54.6 ± 14.3 | 56.8 ± 11.4 | 58 ± 12.6 | 55.6 ± 14.1 | 0.48 |
| BMI (mean ± SD) | 27 ± 4.6 | 26 ± 4 | 26.4 ± 3.5 | 26.1 ± 5.1 | 0.65 |
| ALT (U/L, mean ± SD) | 52.5 ± 59 | 57.5 ± 33 | 52.6 ± 47.9 | 46.2 ± 27.7 | 0.79 |
| AST (U/L, mean ± SD) | 67.1 ± 60 | 77.8 ± 46 | 73.1 ± 52 | 73.5 ± 69 | 0.59 |

CHC: Cirrhosis by hepatitis C virus; AIH: Autoimmune hepatitis; DM: Diabetes mellitus; HBP: High blood pressure; BMI: Body mass index (calculated as patients' body weight divided by the square of the height expressed in kg/m$^2$); MS: Metabolic syndrome.

a criterion of MS; however, it is a common metabolic disturbance in this group of patients. We believe that the higher prevalence of hyperuricemia in CC may be another piece in the puzzle in the relationship between MS, NASH and cirrhosis.

In 1999, Caldwell *et al*[17] described the prevalence of obesity and T2DM in 70 patients with CC, and compared the findings with three patient groups: NASH, cirrhosis with hepatitis C, and primary biliary cirrhosis (PBC). The prevalence of these risks factors (obesity and T2DM) were similar between patients with NASH and patients with CC, both of which had a higher prevalence compared to patients with hepatitis C and PBC. In another study by Poonawala *et al*[16], the prevalence of obesity and T2DM in patients with CC was compared with the prevalence in control patients. The various causes of cirrhosis in the control group were alcohol, chronic viral hepatitis, AIH, PBC and primary sclerosing cholangitis. Similar to the findings by Caldwell *et al*[17], the prevalence of obesity (55% *vs* 24%) and T2DM (47% *vs* 22%) were significantly higher in patients with CC compared with disease controls. Both authors concluded that their data supported the hypothesis that NASH may be an etiological factor in some of the patients with CC[16,17]. We obtained similar results, but in a different population (Mexican Mestizo) and with a bigger sample size. When we classified the patients as CC *vs* no CC, important differences in the prevalence of obesity and T2DM were observed (16.4% *vs* 8.2% and 40% *vs* 22.4%, respectively). However, when patients without CC were classified by etiology, only the prevalence of T2DM was statistically significant (Table 3). With respect to obesity, the prevalence between CC and patients with cirrhosis secondary to alcohol abuse was similar, and both showed a higher frequency than patients with cirrhosis due to hepatitis C and AIH.

An interesting finding in the present study was that patients with CC without a liver biopsy had greater prevalence of MS, obesity and T2DM compared with patients with CC who had a liver biopsy, despite similar liver function tests. This finding may be related to the presence of metabolic disturbances, suggesting to the physician the diagnosis of CC secondary to NASH; thus creating a different situation from patients with CC without metabolic disturbances.

The present study suffered from some limitations. First, the study design. Second, we did not record the waist circumference for the diagnosis of MS, but used BMI as a substitute for waist circumference. The use of BMI may have had a small impact on the number of cases diagnosed with MS, since there is a strong correlation between these parameters ($r = 0.8$)[23,24]. We recognize that this may have resulted in underestimating the number of cases that fulfilled the NCEP definition.

In conclusion, the prevalence of MS, obesity and T2DM in patients with CC is higher than that seen in patients with cirrhosis secondary to others causes. Moreover, the prevalence of hyperuricemia was higher in patients with CC compared to patients with cirrhosis secondary to others causes, a finding not reported previously. Our results support the hypothesis that NASH plays an under-recognized role in some patients with CC.

## COMMENTS

### Background

Nonalcoholic steatohepatitis (NASH) is the main etiology suspected in patients with Cryptogenic Cirrhosis (CC). The association of NASH with Metabolic Syndrome (MS) is well-known; however, the association of CC with MS has not been well examined.

### Research frontiers

The possible association of MS and CC remains unknown.

### Innovations and breakthroughs

This study shows an association between MS with CC, and raises the possibility of an under-recognized role of NASH in CC.

### Applications

Further prospective studies may clarify the association between MS and CC.

### Peer review

The findings in the present study imply that non-alcoholic steatohepatitis is frequently associated with cryptogenic cirrhosis. This paper is well written and the results suggest an under-recognized role of NASH in patients with cryptogenic cirrhosis.

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Este trabajo es de particular interés e importancia. La cirrosis criptogénica es una entidad poco estudiada. En los últimos años se ha considerado que es la resultante de la enfermedad grasa del hígado y que representa uno de los estadios finales de dicho espectro. A pesar de lo anterior existen pocos estudios que relacionen a los padecimientos metabólicos con la cirrosis criptogénica. Este estudio es de los pocos y uno de los primeros datos existentes a nivel mundial en relación con la prevalencia del síndrome metabólico, obesidad y diabetes en el grupo de pacientes con esta enfermedad.

De particular interés es que por primera vez, en este estudio se encontró evidencia de la asociación de la cirrosis criptogénica con la hiperuricemia, lo anterior apoya aun más la fuerte asociación entre los trastornos metabólicos y la cirrosis criptogénica.

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# Utility of endoscopy in patients with incidental gastrointestinal luminal wall thickening detected with CT

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**Abstract**
*Background* Reports of incidental gastrointestinal luminal wall thickening (IGILWT) on computed tomography (CT) in patients without gastrointestinal complaints are not rare. Currently there is no consensus about what to do in those cases. The aim of this study was to evaluate the utility of endoscopic study in asymptomatic patients with IGILWT.
*Material and methods* Retrospective analysis of data obtained prospectively between September 2004 and March 2007 was carried out. Patients without gastrointestinal symptoms/signs with IGILWT and assessed by endoscopy were included. The endoscopic findings were classified as follows: normal, abnormal or nonspecific.
*Results* A total of 10,161 abdominal/pelvic CT scans were performed. Thirty-one patients were included (14 women and 17 men). Median age was 59 years (19–84 years). Distribution of IGILWT along the gastrointestinal (GI) tract was as follows: 1 esophagus, 19 stomach, 1 small-bowel, and 10 colon. Endoscopy was normal in 19 cases (61.2%) and abnormal/nonspecific in 12 cases (38.8%). Nine (29%) patients had cancer as a final diagnosis (gastric cancer in six, colon cancer in two, and non-Hodgkin's lymphoma in one). On multivariate analysis hemoglobin <12 g/dl was the only significant variable to predict an abnormal result by endoscopy.
*Conclusion* Endoscopic study is useful in patients with IGILWT. More than one-third of patients with IGILWT have a significant finding by endoscopic evaluation, mainly cancer. Absence of GI symptoms/signs, age or gender are not valid criteria to decide about further endoscopic evaluation.

**Keywords** Endoscopy · Gastrointestinal wall thickness · Cancer

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Use of computerized tomography (CT) in evaluating patients with various abdominal complaints has been increasing, and consequently reports of incidental gastrointestinal luminal wall thickening (IGILWT) have risen. The clinical significance of this finding remains uncertain and represents a serious problem for the physician.

Despite the clinical problem that IGILWT represents, there are few studies concerning what to do with this radiological abnormality [1–3]. The necessity for clinical guidelines about evaluation of incidental bowel wall thickening on CT scan is evident and urgent. Multiple factors affect the interpretation of gastrointestinal (GI) wall

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thickness, including luminal distension, collapsibility, inhomogeneous filling, comorbidities of the patients, and variations in measurement techniques. There is no radiological criteria to classify, grade or estimate the malignant probability of IGILWT and there is still a significant degree of uncertainty in interpreting this radiologic finding [3, 4]. The aim of our study was to evaluate the usefulness of endoscopic study in patients with IGILWT in terms of its clinical impact and final diagnosis.

## Materials and methods

A retrospective study was developed based on data obtained prospectively in patients with a diagnosis of I-GILWT who had an endoscopic procedure at the Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran (INCMNSZ) between September 2004 and March 2007. Patients were identified through endoscopic reports, and indication of endoscopic procedures in all patients was IGILWT. The definition of IGILWT for this study was wall thickness $\geq$5 mm (esophagus or stomach) or $\geq$3 mm (small bowel and colon), persistent in more of two increments in the presence of good GI distension (qualitative evaluation by radiologist) in subjects without GI signs or symptoms. Associated abnormalities, such as lymphadenopathy and/or mesenteric standing or calcification and fibrofatty proliferation, were not considered for this study. Herein "GI complaints" refers to esophagus, stomach, small-bowel, colon, and/or rectum symptoms and/or signs.

A 16- or a 64-slice multidetector CT (Somatom, Sensation 16 or 64; Siemens München, Germany) was used in the CT examination, and images were obtained with a section thickness of 3–5 mm with a reconstruction interval of 2–2.5 mm. All cases were analyzed on a workstation with the capability to produce coronal reformatted images. For patients who received IV contrast, 120 ml Conray (Mallinckrodt Baker Inc., St Louis, MO, USA) was given 45 s prior to CT examination. Forty milliliters ioditrast M60 (Justesa Imagen Mexicana) was diluted in 1,000 ml water and given to all patients orally 1 h prior to CT. All patients received IV and oral contrast except for those whose serum creatinine was 1.4 mg/dl, who did not receive IV contrast. All CT images were analyzed by at least two certified radiologist and discussed with the endoscopic team before the procedure. All CT and endoscopic studies were carried out in the same center (INCMNSZ).

The endoscopic procedure (gastroscopy or colonoscopy) was chosen according to CT findings. Results were classified as follows: normal (when the endoscopic procedure did not show any abnormality), abnormal (when findings could be associated with findings on CT), or nonspecific (when abnormal findings were not associated with findings on CT). Age, gender, family cancer history, tobacco consumption (yes/no), site of thickness (upper/lower), and hemoglobin level (g/dl) were evaluated as possible variables associated with an abnormal/unspecified endoscopic result. Other issues evaluated were histopathology analysis and impact of endoscopy in the ultimate treatment. All patients with a GI indication for the CT study or a gastrointestinal complaint were excluded. Patients with IGILWT but without endoscopy were excluded of final analysis. Renal disease indications included cystic disease (two patients) and abscess suspected (four patients). Cavernomatous portal degeneration refers to new vessels formed around intrahepatic, extrahepatic biliary tracts and around gallbladder (majorly, vascular plexus of Saint and Petren enlarge and dilate to become large serpentine vessels) after obstruction in portal system [5]. CTs in patients with ovarian cancer were for metastases suspicion. Herein "adrenal pathology" means adenoma suspicion in adrenal glands by treating physician.

All patients were followed up until a definitive diagnosis was made.

### Statistical analyses

Descriptive statistics were used for demographic variables. Results are expressed as medians and ranges. Comparison of quantitative data was performed using Mann–Whitney *U* test. The difference in proportions of categorical data was ascertained by Fisher exact test when the expected number of subjects was less than five, and by chi-square test when the number of subjects in each cell was five or more. Variables with $p < 0.2$ probability of having an abnormal/unspecific endoscopic result in univariate analysis were included in multivariate analyses. Continuous data were categorized into normal and abnormal values for multivariate analysis. Logistic regression was used with a *p*-value $<0.05$ considered as statistically significant. All statistical analyses were conducted using the statistics program SPSS/PC version 12.0 (Chicago, IL, USA).

## Results

During the study period 10,161 abdominal/pelvic CT scans were performed, and 34 with gastrointestinal luminal wall thickening were identified; three patients had GI symptoms and were not included in this study. We evaluated 31 cases for final analysis (prevalence 0.3%). Figure 1 shows CT scans of two of these patients. Fourteen women (45.2%) and 17 men (54.8%) were included (median age 59 years; range 19–84 years). The original indication for the CT scan of all patients is presented in Table 1. The distribution of IGILWTs was esophagus 1 (3.2%), gastric 19 (61.3%),

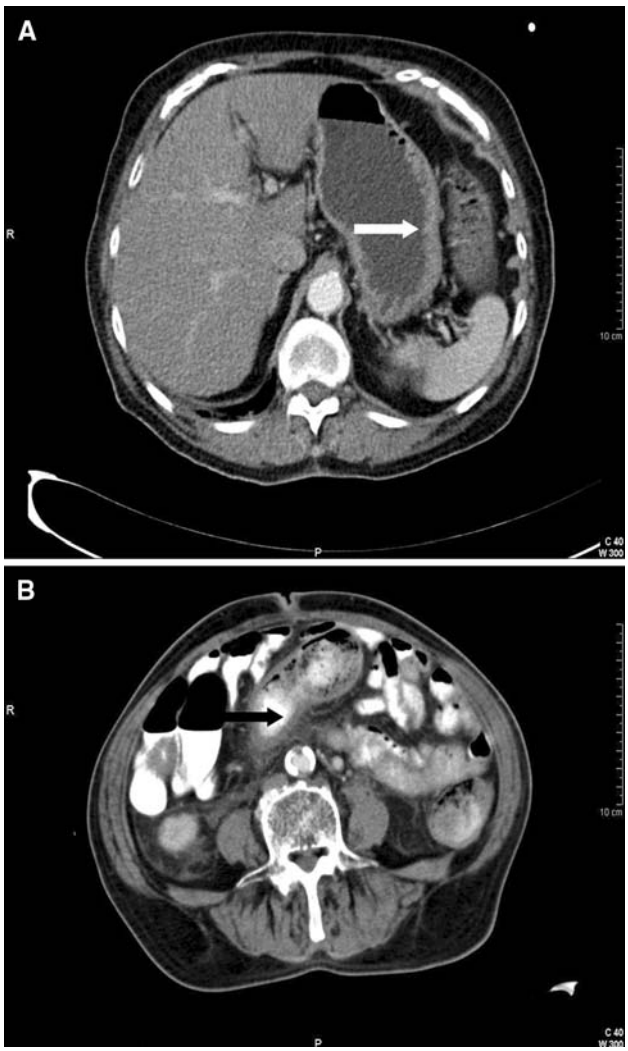


**Fig. 1** Gastrointestinal wall thickness by CT in: **A** stomach and **B** colon, patients 2 and 5

**Table 1** Indications for CT scan in patients with IGILWT

| Indication | *n* (%) |
|---|---|
| Fever of unknown origin | 6 (19.4) |
| Renal disease | 6 (19.4) |
| Adrenal disease | 5 (16.1) |
| Ovarian cancer | 3 (9.7) |
| Cavernomatous portal degeneration | 3 (9.7) |
| Intra-abdominal abscess | 1 (3.2) |
| Hepatic abscess | 1 (3.2) |
| Gunshot | 1 (3.2) |
| Anorexia | 1 (3.2) |
| Nonspecific* | 4 (12.9) |

* When reviewing the chart, no indication for the CT could be identified, nor was any GI complaint recorded

ileum 1 (3.2%), and colon 10 (32.3%). The colon distribution was as follows: cecum 4 (40%), ascendant–transverse–descendent 3 (30%), sigmoid 2 (20%), and rectum 1 (10%). Characteristics of patients according with endoscopic studies results are in Table 2. Four patients with renal diseases had oral contrast only.

Endoscopy was normal in 19 cases (61.3%), abnormal in 10 cases (32.2%), and nonspecific in 2 cases (6.5%). Characteristics and final diagnosis of 12 patients with abnormal/nonspecific result by endoscopy are presented in Table 3. All of them had confirmatory biopsy.

Nine patients had cancer by histopathological analysis, eight had adenocarcinoma, and one non-Hodgkin's lymphoma (five women and four men); six involved the stomach, two the colon, and one ileum. Median age of this subgroup was 53 years (range: 19–84 years) and median hemoglobin was 13.1 g/dl (range: 7.5–16.2 g/dl).

On univariate analysis the factors associated with abnormal/nonspecific endoscopic finding were: gastrointestinal thickness in the colon [relative risk (RR) 5.2; 95% confidence interval (CI) 1.07–25.6; $p = 0.04$] and hemoglobin $\leq$12 g/dl (RR 3.44; 95% CI 1.6–7.7; $p = 0.007$). On multivariate analysis only hemoglobin $\leq$12 g/dl persisted with statistical significance (OR 18; 95% CI 1.72–82, $p = 0.014$) (Table 4). Concordance between radiologists' evaluation was 100%.

All patients with normal findings by endoscopy were followed up for at least 7 months (range: 7–37 months) without any GI complaints.

## Discussion

This series supports that endoscopy is useful in patients with IGILWT and represents the largest sample of patients with IGILWT located in the stomach. Summarizing all previous reports, only 15 patients with IGILWT located in the stomach are analyzed [3]; in this single study we have 19 (Table 5).

Although IGILWT is an important issue, few studies about it exist in the literature [2, 3, 6]. The development of common criteria (in mm) for wall thickening of the GI tract and to assess lumen distention are important issues that need to be addressed to eliminate probable bias that could overestimate the real prevalence of significant findings by endoscopy in IGILWTs. Our study was carried out only with patients without any GI symptoms or associated signs, clear criteria for GI wall thickness, and patients with involvement of both stomach and colon were included. In the study by Bleibel et al. the lack of a clear definition for wall thickening in the GI tract is evident, and comparisons between the groups with normal and abnormal findings in endoscopic studies are not presented.

**Table 2** Characteristics of patients according with endoscopic study result

| Characteristic | Normal endoscopy ($n = 19$), $n$ (%) | Abnormal/unspecific endoscopy ($n = 12$), $n$ (%) | $p$-Value |
|---|---|---|---|
| Female | 11 (58) | 6 (50) | 0.66 |
| Stomach wall abnormalities* | 15 (79) | 5 (42) | 0.04 |
| Previous surgery | 0 (0) | 1 (8) | 1 |
| Familiar cancer antecedents | 8 (42) | 2 (17) | 0.14 |
| Tobacco use | 9 (47) | 5 (42) | 0.75 |
| | Median (range) | Median (range) | |
| Age (years) | 60 (19–80) | 58 (19–84) | 0.77 |
| Hemoglobin (g/dl) | 13.9 (11.4–15.5) | 12.2 (7.5–16.2) | 0.006 |

* Stomach wall abnormalities: IGILWT on stomach

**Table 3** Characteristics and final diagnosis of patients with an abnormal/nonspecific endoscopy result

| | New patient number (old patient number, for illustration only) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Male | | | | | Female | | | | | | |
| | Stomach | | | Colon | | Stomach | | | Colon | | | |
| | 1 (5) | 2 (9) | 3 (12) | 4 (4) | 5 (1) | 6 (7) | 7 (8) | 8 (2) | 9 (6) | 10 (3) | 11 (10) | 12* (11) |
| Age (years) | 33 | 58 | 58 | 33 | 80 | 19 | 63 | 84 | 28 | 50 | 69 | 69 |
| Hb (g/dl) | 9.8 | 9.0 | 7.5 | 8.8 | 13.3 | 13.7 | 16.2 | 14.6 | 15.5 | 13.1 | 13.4 | 11.3 |
| Original indication for CT scan | CPD | UFO | Adr | CPD | Non | Anx | UFO | Rn | CPD | UFO | Adr | Rn |
| Histological diagnosis | Ad | Ad | Ad | CD | AP | Ad | Ad | Ad | Ad | Ad | AP | NLH |

*Hb* hemoglobin, *CPD* cavernomatous portal degeneration, *UFO* unknown fever origin, *Adr* adrenal pathology, *Non* nonspecific, *Anx* anorexia, *Rn* renal pathology, *Ad* adenocarcinoma, *CD* Crohn's disease, *AP* adenomatous polyps, *NLH* nodular lymphoid hyperplasia

* Male patient with involved ileum

**Table 4** Univariate and multivariate analyses for abnormal/nonspecific results on endoscopic procedure

| | $\beta$ coefficient | Standard error | Wald $\chi^2$ | OR (95% CI) | $p$-Value |
|---|---|---|---|---|---|
| *Univariate* | | | | | |
| Age ≥60 years | – | – | – | 0.98 (0.40–2.41) | 1 |
| Sex, male | – | – | – | 1.2 (0.5–2.9) | 0.72 |
| Familiar antecedent | – | – | – | 2.3 (0.63–8.8) | 0.24 |
| Tobacco use | – | – | – | 1.1 (0.46–2.8) | 0.52 |
| Lower GIT, years | – | – | – | 5.2 (1.07–25.6) | 0.05 |
| Hemoglobin ≤12 g/dl | – | – | – | 3.4 (1.6–7.2) | 0.007 |
| *Multivariate* | | | | | |
| Constant | –1.0 | 0.47 | 5.4 | 0.33 | 0.02 |
| Hemoglobin (g/dl) | 2.89 | 1.1 | 6 | 18 (1.7–82) | 0.014 |

*GIT* gastrointestinal thickness

We found that 38.7% of the patients with IGILWTs had significant abnormalities on endoscopy (Table 5). This proportion is less than previous reports. Some possible explanation are: (1) stricter inclusion criteria, (2) the use of a different CT scanner, (3) findings such as esophagitis, hiatal hernia or esophageal varices were not considered for analysis, mainly because we think that these findings may not be the cause of asymptomatic GI wall thickness, (4) the number of cases with gastric affection, and (5) some patients could have been intra-abdominal inflammatory conditions or postoperative CT scans, both of which can have unspecific GI wall thickness due to peri-inflammatory changes or fibrosis associated.

The study by Cai et al. [2] reports a very high prevalence of abnormalities (up to 96% in sigmoid colon and rectum). However, patients with unrelated gastrointestinal symptoms (for example, chronic abdominal pain, chronic abdominal pain, and weight loss, and patients with flank pain) were included; maybe these patients had an indication for an endoscopic procedure. The important issue then

**Table 5** Results of studies for patients with IGILWT

| First author | *N* | Upper, *N* (%) | Colon, *N* (%) | Abnormal/ nonspecific, *N* (%) | Cancer, *N* (%) |
|---|---|---|---|---|---|
| Cai et al. | 67 | 27[a] (40) | 40 (60) | 47 (70) | 4[b] (6) |
| Bleibel et al. | 50 | 16 (32) | 34 (68) | 31 (62) | 6[b] (12) |
| Moraitis et al. | 35 | NI | 35 (100) | 25 (71) | 8 (23) |
| Tellez-Avila et al. | 31 | 20[c] (62) | 11[d] (35) | 12 (39) | 9 (29) |

*NI* not included

[a] Only included patients with pathology of the distal esophagus and stomach

[b] There were no upper GI cancers

[c] Included one patient with esophagus affection

[d] Included one patient with ileum affection

becomes what to do in patients without any clinical indication for an endoscopic procedure. In one of the previous studies, only patients with wall thickness in the colon were included [6] and only in 14 (35%) patients was IGILWT the reason for colonoscopic evaluation. Furthermore, of eight patients with cancer, four had associated GI symptoms or signs.

In our study, stomach cancer was more frequent than colon cancer (absolute frequencies), however when we divided IGILWT into upper and lower GI tract, the percentages of pathological findings were more common in the latter (33% vs. 50%). Results from our study are consistent with data found previously.

Limitations of this study include: only patients with IGILWT and endoscopic studies were included, due to the retrospective design we do not have information about patients with IGILWT who did not undergo endoscopic evaluation, and we have only one patient with esophageal involvement and one patient with small bowel involvement. For this reason it is impossible to form conclusions on these two groups. The reasons why patients with IGILWT could not undergone endoscopic evaluation include: (1) they could have had clinical data which made a more compelling case for further workup, or (2) there was some specific reason for not pursuing endoscopic evaluation (because the CT finding was ignored by the referring clinician, the referring physician found no clinical indication for follow-up, or the patient was lost to follow-up). Initially, 49 (prevalence of 0.48%) patients with gastrointestinal luminal wall thickening were identified; 15 patients did not undergo endoscopic study and were not included in this study. If we consider the 15 patients who did not undergo endoscopy study, the prevalence of significant abnormalities on endoscopy would be 26%. We decided not to use this group for final analysis because the aim of this study was to evaluate endoscopic findings in patients with IGILWT. The use of Somaton Sensation 64-slice multiscanner provides isotropic spatial resolution. This spatial resolution permits coronal-plane reformatted images with an equivalent resolution to the original axial images, which we and others believe may increase diagnostic confidence [7, 8].

The CT scan used for this study provides the function to measure anatomic structures accurately, however the possibility of interobserver variability between the two radiologists could have been presented because of different site measurement, but it did not.

In conclusion, endoscopic studies are useful in patients with IGILWT. More than one-third of patients with IGILWT have a significant finding by endoscopy, mainly cancer, with hemoglobin level being the only significant variable. Absence of GI symptoms/signs, age, and gender are not valid criteria to make a decision on whether or not an endoscopic procedure is indicated.

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El presente estudio representa la respuesta a una situación frecuente en cualquier departamento de endoscopia: que hacer en los pacientes asintomáticos en quienes por un hallazgo incidental en la tomografía se documenta engrosamiento de la pared del tubo digestivo. A pesar de la importancia y alta frecuencia de esta situación , hasta el momento de realizar este estudio solo 3 trabajos previos con pocos pacientes hacían una evaluación al respecto con resultados no consistentes.

Nosotros encontramos que a pesar de que se trataba de pacientes asintomáticos, los pacientes con engrosamiento de la pared gastrointestinal por imagen de tomografía tienen frecuentemente patologías importantes, siendo el cáncer la causa hasta en el 29% de los pacientes y por lo tanto el realizar estudios de endoscopia en estos pacientes se encuentra perfectamente justificado.

**Citas recibidas a este artículo: 3**


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# Utility of a Simplified Predictive Model to Predict Rebleeding in Patients With High-risk Stigmata Ulcers

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**Aim:** To evaluate a simplified Predictive Model (sPM) to predict rebleeding in patients with high-risk stigmata ulcers.

**Patients and Methods:** Retrospectively, patients seen from March 2002 to September 2007 with peptic ulcers Forrest Ia, Ib, IIa and/or IIb were included. A sPM based on modified Blatchford Score Risk System (mBRS) was used.

**Results:** One hundred and seven patients were included. The positive and negative predictive values for rebleeding with mBRS $\leq 1$ were 15% [95% confidence interval (CI): 4-42] and 72% (95% CI: 61-80), respectively; for sPM $\leq 1$ these values were 16% (95% CI: 8-29) and 65.3% (95% CI: 52-76), respectively. The odds ratio for rebleeding in patients with sPM $\leq 1$ was 0.77 (95% CI: 0.6-0.97, $P = 0.03$) and odds ratio for mBRS $\leq 1$ was 0.84 (95% CI: 0.64-1.1, $P = 0.3$).

**Conclusions:** In patients with high-risk stigmata ulcers with sPM and mBRS $\leq 1$ the risk of rebleeding is low and their early discharge could be considered.

**Key Words:** peptic ulcers, endoscopic treatment, active bleeding

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Nonvariceal upper gastrointestinal bleeding is a life-threatening disorder accounting for more than 100,000 admissions per year with a cost of more than $2 billion annually in the United States.[1] There are several score systems to support early discharge of patients with low-risk lesions on endoscopy.[2–4] Although extremely useful, they cannot be completed without the endoscopic findings and, therefore, cannot be used before endoscopy performance. Also, the need for an immediate endoscopy is not possible to be determined with such score systems. Recently, a modified Blatchford Score Risk System[5] (mBRS) which exclude the endoscopy findings was reported with good results to identify patients with gastrointestinal bleeding with a low likelihood of having high-risk stigmata ulcers (HRSU) and a low risk of adverse outcomes (rebleeding and death).

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The aim of this study is to evaluate a new simplified Predictive Model (sPM) to predict rebleeding in patients with HRSU. A secondary aim is to evaluate sPM to predict mortality in patients with HRSU.

## PATIENTS AND METHODS

We retrospectively reviewed data obtained prospectively (electronic and paper-based records) of patients with HRSU who underwent an endoscopy at the Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán" from February 2002 to September 2007. For this study, HRSU was defined as patients with hemorrhage from peptic ulcer disease (gastric or duodenal) with major bleeding stigmata, defined by groups according to Forrest's classification[6]: Ia (spurting hemorrhage), Ib (oozing hemorrhage), IIa (nonbleeding visible vessel), and IIb (adherent clot). Patients with hematemesis and those who were hemodynamically unstable underwent an endoscopy after initial resuscitation. A regular diagnostic endoscope was initially used (GIF-100, GIF-130, GIF-140, or GIF-160, Olympus, Japan) and the therapeutic modality (monotherapy or dual) was assigned according to physician criteria. Aside from epinephrine injection, endoscopic therapy (ET) was performed either with heat probe coagulation, Argon plasma coagulation, or hemoclips (Olympus, Japan). All conscious patients were sedated with midazolam, phentanyl, and/or propofol. Informed consent was obtained before the procedure in all patients.

Recurrent bleeding was clinically defined as the presence of hematemesis or melena, or both, coupled with the development of shock or decrease in hemoglobin concentration by at least 2 g/dL after initial stabilization of 24 hours or aspiration of fresh blood from nasogastric tube.[7,8] Bleeding was confirmed by endoscopy or surgery in all cases. Clinical, laboratory, and demographic characteristics were recorded as well as Forrest's classification, mBRS, the initial endoscopic technique for hemostasis, rebleeding, requirement for surgery, blood transfusion, and mortality during the first 30 days after the procedure. Monotherapy was defined as epinephrine injection alone on a 1:10,000 dilution. Dual therapy was considered when, besides epinephrine injection, other ET method was used (heat probe, argon plasma coagulation, or hemoclips).

### Predictive Models

According to the mBRS,[5] different punctuation to hemoglobin levels is assigned as well as some clinical variables and comorbidities (Table 1), however, for final analysis patients are classified as a mBRS $\leq 1$ (low risk) and patients with a mBRS $\geq 2$ (high risk). In this work we

**TABLE 1.** The Modified Blatchford Risk Score

| | Points Assigned | | | | |
|---|---|---|---|---|---|
| **Variable** | **0** | **1** | **2** | **3** | **6** |
| Hemoglobin level (g/dL) | | | | | |
| Men | ≥13.0 | 12.0-12.9 | — | 10.0-11.9 | <10.0 |
| Women | ≥12.0 | 10.0-11.9 | — | — | <10.0 |
| Systolic blood pressure (mm Hg) | ≥110 | 100-109 | 90-99 | <90 | — |
| Heart rate (beats/min) | <100 | ≥100 | — | — | — |
| Melena | No | Yes | — | — | — |
| Liver disease | No | — | Yes | — | — |
| Cardiac failure | No | — | Yes | — | — |

adapted this punctuation and only considered one cut-off point for each one of the variables to make easier for clinicians to perform the analysis. The sPM is explained in Table 2. We defined a low sPM as ≤1, otherwise it was considered as high risk (≥2).

## Statistical Analysis

Results are expressed as means and ±SD or as a medians and ranges according to distribution. Comparison of quantitative data was performed using the Student *t* test or Mann-Whitney *U* test. The differences between proportions of categorical data were obtained by the Fisher exact test when the number of expected patients was <5 and by the $\chi^2$ test otherwise. Predictive values were used to evaluate the utility of the model to predict rebleeding and mortality. Multivariate logistic regression models were used to assess the independent association between mBRS/sPM of ≤1 and the occurrence of rebleeding or mortality. A *P* value <0.05 was considered statistically significant. All statistical analyses were conducted using the statistics program SPSS/PC version 12.0 (Chicago, IL).

# RESULTS

During the study period, 107 patients with HRSU were admitted to our hospital. Fifty women (46.7%) and 57 men (53.3%) were included, with a mean age of 57.3 ± 17.1 years. Clinical, demographic, and laboratory characteristics in low risk versus high-risk patients are shown in Table 3. The most common localization of HRSU was the stomach, and Forrest IIa was the most frequent (39.3%) lesion. A total of 45 (42.1%) patients received proton pump inhibitors at the moment of the event; 42 (39.3%) patients had previous peptic ulcer disease (according to paper-based records); and 26 (24.3%) patients were positive to histological examination for *Helicobacter pylori* infection. The median number of endoscopic procedures by patient was 2 (range: 1 to 4). Median epinephrine volume injected was 12 mL (range: 2 to 40 mL). The median (range) of blood units transfused was 1 (0 to 6).

Initial success for endoscopic hemostasis was achieved in 98 patients (91.6%). Fifty (51%; 50 of 98) patients received dual ET and 48 (48.9%) patients underwent single therapy. Hemostasis was not possible in 9 (8.4%) patients who underwent surgery immediately. Four of them subsequently died (between 1 and 20 d after surgery). Recurrent bleeding was documented in 26 of 98 (26.5%) patients, with a median time of 2 (range: 1 to 40 d) days. Success was achieved in 20 patients. Six patients underwent emergency surgery owing to recurrent bleeding. Mortality was 18.7% (20 patients), although only in 7 patients the cause of death was related to ulcer bleeding (6.5%) with a follow up of 30 days.

**TABLE 2.** Simplified Predictive Model for Predict Rebleeding in High-risk Stigmata Ulcers

| | Points Assigned | |
|---|---|---|
| **Variable** | **0** | **1** |
| Hemoglobin level (g/dL) | | |
| Men | >10.0 | ≤10.0 |
| Women | >10.0 | ≤10.0 |
| Systolic blood pressure (mm Hg) | >90 | ≤90 |
| Heart rate (beats/min) | <100 | ≥100 |
| Melena | No | Yes |
| Liver disease | No | Yes |
| Cardiac failure | No | Yes |

## Predicting Rebleeding

The mBRS ≤1 compared with mBRS ≥2 was not associated with lower risk of rebleeding (15.3% vs. 28.2%; $P = 0.27$). Regarding sPM, patients with ≤1 had a rebleeding rate of 17% versus 35.2% in patients with score ≥2, $P = 0.041$. The odds ratio (OR) for rebleeding in patients with mBRS ≤1 and sPM ≤1 are shown in Table 4. In multivariate analyses, only sPM has independent statistical significance [OR: 1.80 (95%confidence: 1.1%-2.9%); $P = 0.018$]. The positive and negative predictive values for rebleeding in patients with mBRS ≤1 and sPM ≤1 are shown in Table 5.

## Predicting Mortality

A low mBRS was not associated with a lower mortality (18.7% vs. 18.6%, $P = 0.6$), on the other hand, a low sPM was statistically associated with this outcome (9.8% vs. 26.7%, $P = 0.028$). The OR for mortality in patients with mBRS ≤1 and sPM ≤1 can be observed in Table 4. For mortality, the positive and negative predictive values in patients with the mBRS ≤1 and sPM ≤1 are shown in Table 5.

# DISCUSSION

In this study we present 2 useful Risk Score Systems to predict rebleeding after ET in patients with HRSU. There are some score systems to detect patients with high risk of mortality and recurrence bleed.[3,4] Until this moment all score systems used include multiple parameters that are difficult to remember and to obtain in daily clinical scenario. Because of this, our aim was to offer to the physicians a useful clinical tool to detect patients with low risk of adverse outcomes and the possibility of early discharge.

According to our results, the sPM is a useful score for predicting rebleeding and mortality. The sPM offers some advantages over other scores: (1) it is easier to obtain, (2) easier to use, and (3) easier to remember. Because the parameters used in sPM are mainly clinical features and hemoglobin level, we assume that this score is available everywhere. The sPM use simple punctuation (0 and 1) for all variables, so their use is very simple and practical. All parameters considered in the sPM are basic clinical

**TABLE 3.** Characteristics, Success of Endoscopic Treatment, and Requirement of Surgery in Low-risk (≤1) Versus High-risk (≥2) Patients

| | mBRS | | | sPM | | |
|---|---|---|---|---|---|---|
| **Variable** | **Low Risk N = 16 n (%)** | **High Risk N = 91 n (%)** | ***P*** | **Low Risk N = 51 n (%)** | **High Risk N = 56 n (%)** | ***P*** |
| Female | 7 (44) | 43 (47) | 1 | 20 (39) | 30 (54) | 0.23 |
| Forrest Ia/Ib | 4 (25) | 25 (27) | 0.9 | 13 (26) | 16 (29) | 1 |
| Proton pump inhibitors use | 5 (31) | 40 (44) | 0.23 | 25 (49) | 20 (36) | 1 |
| *Helicobacter pylori* infection | 5 (31) | 21 (23) | 0.10 | 15 (29) | 11 (20) | 0.36 |
| Endoscopic treatment, monotherapy | 10 (63) | 38 (42) | 0.08 | 20 (39) | 28 (50) | 0.69 |
| Initial endoscopic hemostasis | 13 (81) | 85 (93) | 0.94 | 47 (92) | 51 (91) | 0.40 |
| Requirement for surgery | 3 (19) | 12 (13) | 0.58 | 5 (10) | 10 (18) | 0.22 |
| NSAID | 5 (31) | 28 (31) | 0.73 | 13 (25) | 20 (36) | 0.49 |
| Antiplatelet agents | 5 (31) | 9 (10) | 0.009 | 9 (18) | 5 (9) | 0.14 |
| Oral anticoagulation | 2 (13) | 8 (9) | 0.53 | 3 (6) | 7 (13) | 0.32 |
| | X ± SD | X ± SD | | X ± SD | X ± SD | |
| Age (y) | 60.3 ± 16 | 56.6 ± 17 | 0.44 | 59 ± 15.7 | 55.4 ± 18.2 | 0.11 |
| | Median (Range) | Median (Range) | | Median (Range) | Median (Range) | |
| Endoscopies | 1 (1-1) | 2 (1-7) | 0.49 | 2 (1-3) | 2 (1-7) | 0.12 |
| Blood units transfused | 0 (0-2) | 1 (0-6) | 0.03 | 0 (0-4) | 1 (0-3) | 0.01 |
| Epinephrine volume (mL) | 12 (5-26) | 12 (5-40) | 0.47 | 12 (5-30) | 12 (5-20) | 0.35 |

mBRS indicates modified Blatchford Risk Score System; NSAID, nonsteroidal anti-inflammatory drug; sPM, simplified Predictive Model.

parameters for critical patients and important comorbidities. Both scores evaluated in this study, although similar, have some important differences among them: (1) the mBRS considers different punctuation to different hemoglobin levels as well as some clinical variables and comorbidities and (2) in sPM only one cut-off point for each one of evaluated variables is considered. The differences observed between the 2 models to predict rebleeding and mortality are interesting. Even though the sPM is derived from mBRS, the κ value is low ($k = 0.32$; disagreement in 35 patients). This could be explained because differences in given points for each variable in the 2 different scores (ie, a patient with liver disease, or cardiac disease, or SBP $< 100$ mm Hg, or man with hemoglobin $< 12$ g/dL, are considered in high risk according to mBRS, whereas according to sPM these patients remain in the low-risk group). These differences are favorable to sPM use.

**TABLE 4.** Summary of Univariate and Multivariate Analysis for Risk of Rebleeding and Mortality

| **Variable** | **Odds Ratio (95% Confidence Interval)** | ***P*** |
|---|---|---|
| Univariate | | |
| Rebleeding outcome | | |
| mBRS ≤1 | 0.84 (0.64-1.1) | 0.31 |
| sPM ≤1 | 0.77 (0.6-0.97) | 0.032 |
| Monotherapy | 0.62 (0.25-1.5) | 0.36 |
| Age ≥60 y | 0.67 (0.27-1.6) | 0.49 |
| Forrest Ia/Ib | 1.33 (0.49-3.5) | 0.6 |
| Mortality outcome | | |
| mBRS ≤1 | 1.03 (0.77-1.3) | 0.5 |
| sPM ≤1 | 0.79 (0.66-0.95) | 0.017 |
| Monotherapy | 0.56 (0.21-1.5) | 0.32 |
| Age ≥60 y | 0.78 (0.29-2) | 0.8 |
| Forrest Ia/Ib | 1.5 (0.56-4.4) | 0.4 |
| Multivariate | | |
| Rebleeding outcome | | |
| sPM ≤1 | 0.3 (0.11-0.8) | 0.02 |
| Mortality outcome | | |
| sPM ≤1 | 0.07 (0.01-0.62) | 0.016 |

mBRS indicates modified Blatchford Risk Score System; sPM, simplified Predictive Model.

Our results are similar to some reports on recurrent bleeding, emergency surgery, and mortality rates,[8] but are still slightly higher in respect to other foreign referral centers.[7] Nowadays, dual therapy in endoscopy is the most accepted treatment owing to HRSU. This modality has shown to be better when compared with epinephrine injection alone for reducing further bleeding, the need for emergency surgery, and mortality.[8–11] According to our results, there was no correlation between recurrent hemorrhage and need for emergency surgery with the use of monotherapy versus dual ET. We consider that this finding is due to the sample number and do not reflect the best feasible results with single ET, compared with other worldwide centers. The same phenomenon was observed in a previous work from our group.[12] Interestingly, regardless that sample number was insufficient to obtain statistical difference among dual versus single ET (a well-known factor), this sample was enough to detect differences regarding sPM values to predict rebleeding.

Some limitations of our study are: (1) the endoscopic procedures were not videotaped, so we cannot reevaluate the accuracy of initial diagnosis (it is well known the poor interobserver reliability of stigmata recognition[13]), (2) although the patients were enrolled as a prospective cohort, the conclusions of this study are limited by the fact that they are based on retrospective analysis, and (3) the medium sample size. It is important to mention that despite sample size, the sPM had power to detect differences regarding rebleeding risk contrary to mBRS. Despite retrospective design and sample size, this is an important world-wide topic and information from other Latin American centers will be useful to improve quality and increase survival in this kind of patients.

In conclusion, in patients with HRSU with sPM and mBRS ≤1 the risk of rebleeding is low and their early discharge could be considered. It is possible to simplify the mBRS without loss of their predictive values. More studies with a prospective design and a larger sample size are necessary to corroborate these findings.

**TABLE 5.** Predictive Values of mBRS and the sPM for Rebleeding and Mortality in Patients With High-risk Stigmata Ulcers

| | mBRS ≤1 | | | | Simplified Predictive Model ≤1 | | | |
|---|---|---|---|---|---|---|---|---|
| **Outcome** | **PPV** | **95% CI** | **NPV** | **95% CI** | **PPV** | **95% CI** | **NPV** | **95% CI** |
| Rebleeding | 15 | 4-42 | 72 | 61-80 | 16 | 8-29 | 65 | 52-76 |
| Mortality | 21 | 8-48 | 81 | 71-88 | 9 | 3-20 | 73 | 60-83 |

CI indicates confidence interval; mBRS, modified Blatchford Risk Score System; NPV, negative predictive value; PPV, positive predictive value; sPM, simplified Predictive Model.

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El trabajo fue dirigido a evaluar la utilidad de un sistema de puntuación para determinar que pacientes con úlceras de alto riesgo podían presentar recurrencia de sangrado. Aunque múltiples sistemas de puntuación han sido reportados todos son muy complejos y los parámetros necesarios no están disponibles en todos los hospitales. Nuestro sistema únicamente toma en cuenta características clínicas y resultados de biometría hemática.

Encontramos que el sistema propuesto por nuestro grupo fue tan efectivo como los más utilizados en otros países con la ventaja de una mayor facilidad y disponibilidad prácticamente en cualquier hospital.

Citas recibidas de otros autores a este trabajo: cero

# Endoscopic ultrasound-guided biliodigestive drainage is a good alternative in patients with unresectable cancer

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A total of 11 prospective cases of endoscopic ultrasound (EUS)-guided cholangio-drainage (EUCD) in patients with end-stage biliopancreatic cancer and biliary tract obstruction are reported. Other available drainage methods (endoscopic retrograde cholangiopancreatography and/or percutaneous transhepatic biliary drainage) of the biliary tract were attempted without success prior to EUS. Technical and clinical success was achieved in 10/11 patients (91%) and in 9/10 patients (90%), respectively. Bilirubin decreased by more than 50% in 7/11 patients (64%). One patient had a complication that required re-intervention and another patient developed biloma. No mortality directly related to the procedure was documented. In conclusion, EUCD is a good alternative for patients with malignant obstruction of the biliary tract in whom other drainage methods have failed.

## Introduction

Biliary drainage by endoscopic retrograde cholangiopancreatography (ERCP) is a well accepted palliative treatment in patients with malignant stricture; however sometimes it is not possible to perform it successfully [1]. In patients who are at high risk for surgery, mortality, or other situations, other alternatives are available, such as percutaneous transhepatic biliary drainage (PTBD), although this has a high complication rate [1].

The proximity of the endoscopic ultrasound (EUS) device to the obstruction area results in a higher resolution than would be achieved by computed tomography or magnetic resonance imaging. Furthermore, EUS is a minimally invasive procedure with a lower complication rate compared with ERCP. In the world literature there are scarce data on EUS-guided cholangio-drainage (EUCD) [1–10].

The aim of this study was to assess the use of EUCD in patients with extrahepatic bile duct obstruction in whom ERCP had failed.

## Patients and methods

### Patients

Prospectively consecutive patients were included from March 2007 to June 2010. All patients had extrahepatic bile duct obstruction secondary to unresectable malignant tumor (pancreatic cancer, cholangiocarcinoma, malignant tumor of ampulla of Vater, or metastases), and at least one ERCP with precut was attempted before EUCD. Written informed consent was obtained from each patient before the procedure.

### Methods

Before each procedure, complete blood count, international normalized ratio, and prothrombin time were obtained for all patients to minimize the risk of bleeding. An endoscopist who was experienced in EUS (M.A.R.L.) performed the EUCD in all cases. The procedures were performed under deep sedation with midazolam, propofol, and fentanyl administered by an anesthesiologist. A convex linear-array GF-UCT140 echoendoscope (Olympus Corp., Tokyo, Japan) with an Aloka console SSD-5500 (Aloka Co., Ltd., Tokyo, Japan) were used. Supplemental oxygen was provided by means of nasal prongs. All patients were hospitalized and remained so for at least 4 hours after the procedure for observation with automatic monitoring in case of complications.

Technical success was defined as the proper positioning of one or more plastic stents with the echoendoscope either via a transgastric or transduodenal technique. Clinical success was defined as a reduction or disappearance of jaundice and a lack of septic response, or a bilirubin decrease of about 50% or more. Follow-up was made at least 1 month after the procedure.

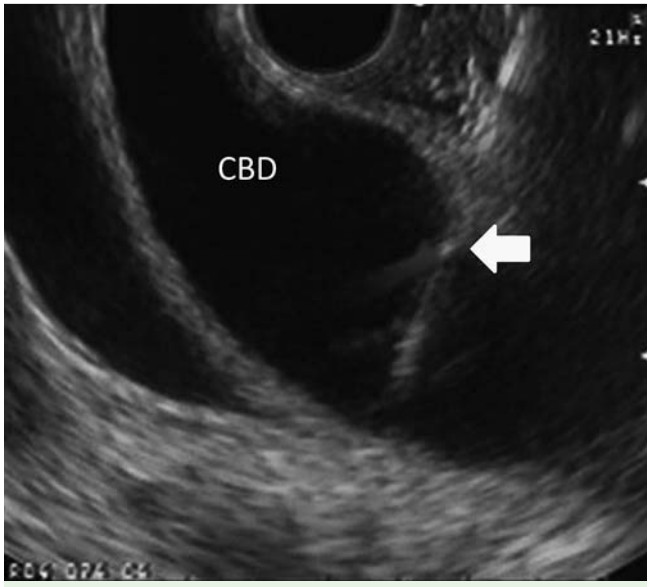


**Fig. 1** Convex echoendoscope located in the apex of the duodenal bulb. A 19-G fine-needle aspiration (FNA) needle (white arrow) is inserted into the dilated common bile duct (CBD) just above of the distal obstruction.

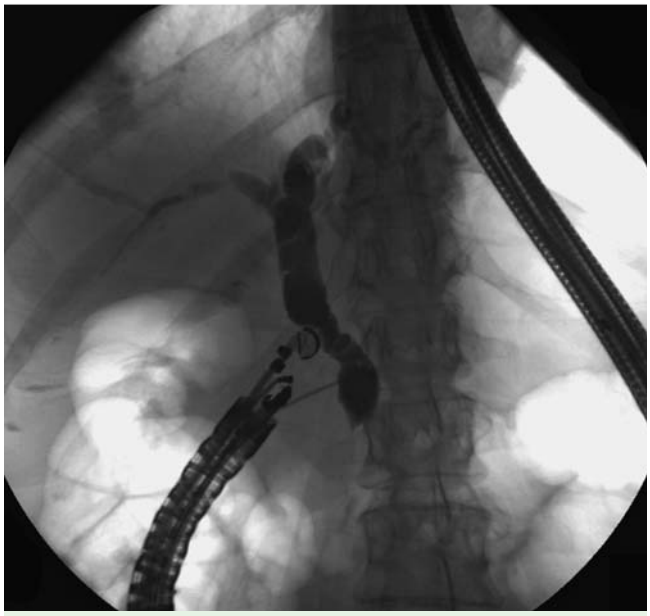

**Fig. 2** Cholangiogram obtained by endoscopic ultrasound-guided puncture. There is a stricture of the distal common bile duct with proximal dilation.

## Technique

### EUS-guided choledochoduodenostomy (EUS–CD)

After prophylactic administration of intravenous ceftazidime 1 g single dose, the dilated extrahepatic bile duct was visualized and punctured with a 19-G fine-needle aspiration (FNA) needle (Echo-Tip 19G; Cook Medical Endoscopy, Winston-Salem, North Carolina, USA) from the duodenal bulb (▶ **Fig. 1**).

After the bile was aspirated, contrast medium was injected to obtain a cholangiogram (▶ **Fig. 2**), and a 0.035-inch guide wire was inserted into the bile duct via the FNA needle.

In some cases, after removal of the FNA needle, a needle knife was inserted over the guide wire and the output current mode was set to create a bigger choledochoduodenal fistula. Tapered biliary dilation catheters, 6 Fr, 7 Fr, and 10 Fr (Soehendra biliary dilation catheters, Cook Medical Inc., Bloomington, Indiana, USA) or 8-mm biliary balloon dilator (Max Force, Microvasive, Boston, Massachusetts, USA) were used for dilation of the choledochoduodenal fistula. Finally a pigtail plastic stent was inserted (▶ **Fig. 3**).

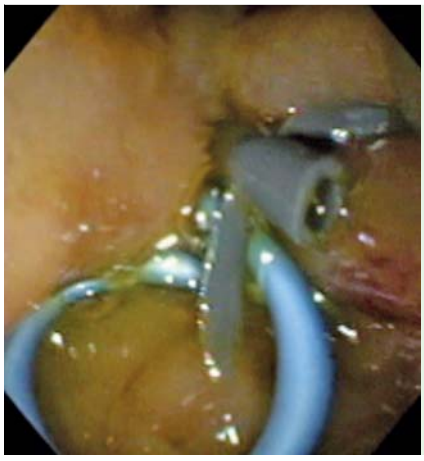

**Fig. 3** A 7-Fr straight stent and double pigtail plastic stent are seen through the choledochoduodenostomy into the dilated extrahepatic bile duct.

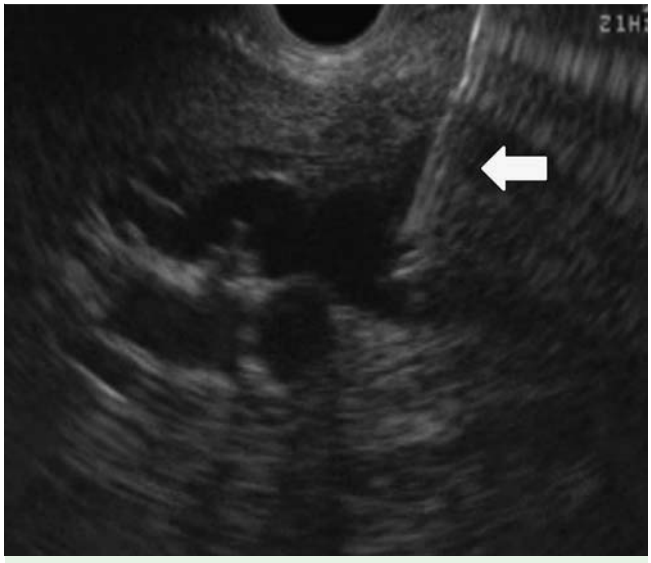

**Fig. 4** The dilated peripheral branch of the left intrahepatic system is accessed transgastrically by using a 19-G fine-needle aspiration needle (white arrow).

### EUS-guided hepaticogastrostomy (EUS–HG)

EUS–HG was completed in a similar fashion to EUS–CD but with the EUS scope placed against the lesser curve of the stomach and a direct puncture made to the dilated left intrahepatic biliary system. The transmural tract was dilated by using a 6-Fr and 7-Fr Soehendra bougie, and a plastic stent with a pigtail was deployed (▶ **Figs. 4 – 6**).

Patients with cholangitis received ceftriaxone 1 g i. v. twice daily and metronidazole 500 mg i. v. three times daily for 7 days. Ceftazidime was not used for prophylaxis in these patients.

## Statistical analysis

Descriptive statistics for nonparametric distribution were used (median and ranges, relative frequencies, and absolute frequencies).

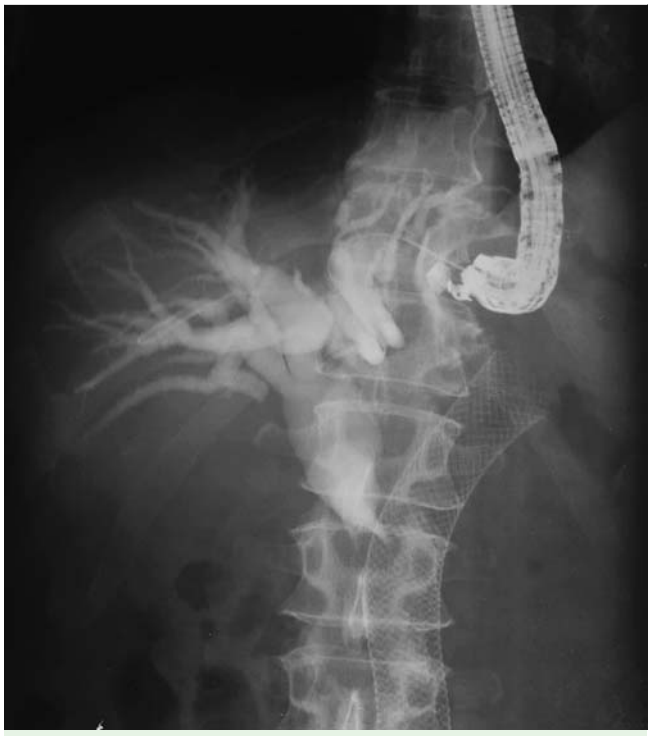

**Fig. 5** A 0.035-inch guide wire is advanced through the fine-needle aspiration needle into the left intrahepatic system. A duodenal metallic stent had been placed previously because of duodenal obstruction.

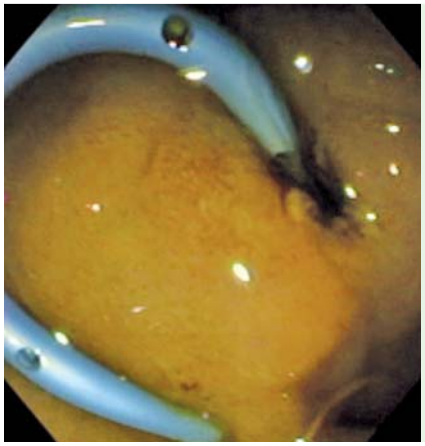

**Fig. 6** A plastic stent with a pigtail is transgastrically deployed into the left intrahepatic system.

## Results

Over 39 months, 11 patients were included in the study, eight of whom (72.7%) were men. Median age was 58 years (range 20–84 years). Of the included patients, five (45.4%) had unresectable pancreatic cancer, three (27.3%) had unresectable cholangiocarcinoma, one patient had a neuroendocrine tumor (9.1%), another patient (9.1%) had a malignant tumor of the ampulla of Vater, and one patient (9.1%) had metastases. The median number of attempted ERCPs before EUCD was 2 (range 1–3). The clinical and demographic characteristics of the patients, including lesions and devices, are shown in **Table 1**.

The procedure was technically successful in 10/11 patients (90.9%), but with clinical and laboratory resolution in only 9/10 (reduction/disappearance of jaundice and lack of septic response). Decreased bilirubin levels were seen in all patients (**Table 2**).

A total bilirubin decrease of more than 50% was observed in 7/11 patients (63.6%), and a direct bilirubin decrease of more than 50% was observed in eight patients (72.7%).

Two (18.2%) complications were seen: one patient had a stent migration to the stomach (patient #8) that required re-intervention for stent replacement. This patient presented with cholangitis and septic shock before the first stent placement and, despite two interventions, continued to experience septic shock; he died 4 days after being admitted. In one case (patient #11), a third-space leak (biloma, 3 cm diameter) occurred during the procedure and was treated with PTBD. Stent withdrawal was not required in any patient. No stent occlusion occurred in any patient and none of the patients showed clinical signs of peritonitis during follow-up.

## Discussion

The case series presented adds evidence to the utility of EUCD. In the world literature to date, EUCD has been described in 64 patients with malignant obstruction (**Table 3**).

EUS-guided cholangiography and pancreaticography were first described by Wiersema et al. [4]. Subsequently EUS-guided transmural biliary drainage was reported by Giovannini et al. [5] as well as by Burmester [6]. In our series the technical success achieved was 91% (10/11) and the complication rate was 18% (2/11). The success rates in previous reports are similar to ours

**Table 1** Clinical and demographic characteristics of included patients, endoscopic ultrasound findings and stents.

| Patient # | Sex/age, years | Derivation modality | Bile duct diameter, mm | Stent size, cm | Stent lumen diameter, Fr | Initial stent |
|---|---|---|---|---|---|---|
| 1 | M/58 | Choledochoduodenostomy | 12 | 5 | 8 | Plastic DPT |
| 2 | M/63 | Choledochoduodenostomy | 15 | 4 | 10 | Plastic DPT |
| 3 | F/82 | Choledochoduodenostomy | 13 | 4 | 10 | Plastic DPT |
| 4 | M/69 | Choledochoduodenostomy | 16 | 5 | 7 | Plastic DPT |
| 5 | M/69 | Hepaticogastrostomy | 16 | 5 | 7 | Plastic DPT |
| 6 | F/52 | Choledochoduodenostomy | 14 | 4 | 7 | Plastic SPT |
| 7 | M/45 | Choledochoduodenostomy | 14 | 4 | 7 | Plastic DPT |
| 8 | M/84 | Hepaticogastrostomy | 16 | 5 | 7 | Plastic DPT |
| 9 | M/45 | Choledochoduodenostomy | 15 | 4 | 7, 10 | Plastic DPT |
| 10 | F/37 | Choledochoduodenostomy | 15 | 4 | 7, 10 | Plastic DPT |
| 11 | M/20 | Choledochoduodenostomy | 15 | – | – | – |

DPT, double pigtail; SPT, single pigtail.

**Table 2** Final outcome of included patients.

| Patient # | Tumor/size, mm | Total bilirubin, mg/dL | | Patient with cholangitis | Technical results | Complications | 1-month outcome (clinical results) | Time to death, days |
|---|---|---|---|---|---|---|---|---|
| | | Pre- | Post- | | | | | |
| 1 | Pancreas (45 × 35) | 15.2 | 1.28 | No | Success | None | Alive | 71 |
| 2 | Pancreas (60 × 40) | 15.3 | 9.9 | No | Success | None | Alive | 36 |
| 3 | Pancreas (50 × 45) | 11.3 | 1.47 | No | Success | None | Alive | 87 |
| 4 | Pancreas (40 × 35) | 10 | 2.1 | No | Success | None | Alive | 47 |
| 5 | Pancreas (40 × 40) | 11.2 | 3 | No | Success | None | Alive | 40 |
| 6 | Metastases (50 × 50) | 6.3 | 1.6 | Yes | Success | None | Died* | 12 |
| 7 | Cholangiocarcinoma (30 × 25) | 21.5 | 11 | No | Success | None | Alive | 70 |
| 8 | Cholangiocarcinoma (40 × 35) | 20 | 14† | Yes | Success | Stent migration‡ | Died | 4 |
| 9 | Cholangiocarcinoma (30 × 25) | 18 | 17 | Yes | Success | None | Alive | 160 |
| 10 | Malignant tumor of ampulla of Vater (–) | 12.8 | 2.7 | No | Success | None | Alive | 240 |
| 11 | Neuroendocrine tumor (35 × 30) | 27.4 | 15 | Yes | Failure | Biloma | Alive | 120 |

*Not related to biliary obstruction.
† Control liver function test 3 days after procedure.
‡ Migration to the stomach. Re-intervention needed for a new EUS-HG. The second intervention was technically successful.

**Table 3** Reported cases with therapeutic endoscopic ultrasound (EUS)-guided choledochoduodenostomy and EUS-guided hepaticogastrostomy (excluding patients with rendezvous technique).

| First author, year | n | Device for puncture | Technical success, n | Clinical success, n | Initial stent | Early complications (n) |
|---|---|---|---|---|---|---|
| **EUS-guided choledochoduodenostomy** | | | | | | |
| Giovannini, 2001 [5] | 1 | Needle knife | 1/1 | 1/1 | 10-Fr plastic | None |
| Burmester, 2003 [6] | 2 | 19-G fistolotome | 1/2 | 1/1 | 8.5-Fr plastic | Bile peritonitis (1) |
| Puspok, 2005 [12] | 5 | Needle knife | 4/5 | 4/4 | 7 – 10-Fr plastic | None |
| Kahaleh, 2006 [8] | 1 | 19-G fine needle | 1/1 | 1/1 | 10-mm metal | Pneumoperitoneum |
| Yamao, 2006 [16] | 5 | Needle knife | 5/5 | 5/5 | 7 – 8.5-Fr Plastic | Pneumoperitoneum (1) |
| Ang, 2007 [17] | 2 | Needle knife | 2/2 | 2/2 | 7-Fr plastic | Pneumoperitoneum (1) |
| Fujita, 2007 [18] | 1 | 19-G fine needle | 1/1 | 1/1 | 7-Fr plastic | None |
| Tarantino, 2008 [19] | 4 | 19-G, 22-G fine needle/needle knife | 4/4 | 4/4 | Plastic* | None |
| Itoi 2008 [20] | 4 | Needle knife (2), 19-G fine needle (2) | 4/4 | 4/4 | 7-Fr plastic (3), naso-biliary drainage (1) | Bile peritonitis (1) |
| Hanada, 2009 [21] | 4 | 19-G fine needle | 4/4 | 4/4 | 6 – 7-Fr plastic | None |
| Park, 2009 [22] | 4 | 19-G fine needle/ needle knife | 4/4 | 4/4 | 10-mm covered metal stent | None |
| Brauer, 2009 [15] | 3 | 19-G, 22-G fine needle/needle knife | 2/3 | 2/2 | 10–Fr plastic | Pneumoperitoneum, cardiac and respiratory failure |
| **EUS-guided hepaticogastrostomy** | | | | | | |
| Burmester, 2003 [6] | 1 | 19-G fistolotome | 1/1 | 1/1 | 8.5-Fr plastic | None |
| Kahakeh, 2006 [8] | 2 | 19-G, 22-G fine needle | 2/2 | 2/2 | 10-Fr plastic | None |
| Artifon, 2007 [23] | 1 | 19-G fine needle | 1/1 | 1/1 | 10-mm covered metal stent | None |
| Bories, 2007 [10] | 11 | 19-G, 22-G fine needle/cystotome | 10/11 | 10/10 | 7-Fr plastic, 10-mm covered metal stent | Plastic (1),† covered metal stent (3)‡ |
| Will, 2007 [13] | 4 | 19-G fine needle | 4/4 | 3/4 | 10-mm metal stent, covered metal stent | Cholangitis (1) |
| Park, 2009 [22] | 9 | 19-G fine needle/ needle knife | 9/9 | 9/9 | 10-mm covered metal stent | None |

*Unspecified.
† Ileus.
‡ Biloma, stent migration, and cholangitis.

[7 – 14], but importantly, in the present report "clinical success" was achieved in 90 % of patients (9/10). Because all of our patients had a terminal disease with a short expected survival, the extent of the follow-up is relatively short, but unlike other reports, we clearly defined this time.

In the first report by Giovannini et al. [5], a 6.5-Fr Soehendra dilator was used to increase the size of the fistula between the duodenal lumen and the bile duct to facilitate passage of other accessories. After that, a variety of standard biliary catheter and pneumatic dilators was used with selection based on patient anatomy. No formal comparative trials exist to clarify the relative utility of these devices. Equipment use varies among endoscopists and often requires trial and error, even within the same patient. In the near future, development of equipment specifically designed for this purpose (EUCD) will allow improved performance of the procedure.

Plastic stents were used in the present study. It is well known that repeated interventions could be required with plastic stents for exchange and eventual stent removal. This could be avoided with metal stents. By extrapolation with bile duct malignant obstruction and ERCP, we decided to use plastic stents because all of our patients were being treated palliatively and had an expected survival of less than 6-months. Although in this study stent occlusion did not occur, the stents could be electively replaced at periodic intervals if necessary according to endoscopist preference. Regarding the technique, in the first three cases the penetration of the duodenum with the dilation catheters was difficult; in the following six cases, after removal of the FNA needle, a needle knife was inserted over the guide wire and the output current mode was set to increase the size of the fistula before finally dilating it with an 8-mm balloon. We found this sequence was the best to facilitate the positioning of the stent. We did not encounter the same problem using EUS–HG.

The main limitation of this study is the design and sample size. All previous studies are mainly case reports and few report samples sizes over 10 patients [4, 7, 10]. In the future a randomized trial comparing PTBD with EUCD will be useful. In conclusion, we have shown that the EUCD is technically feasible and relatively safe in selected patients with malignant causes of biliary obstruction.

**Competing interests:** None

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Los pacientes con obstrucción maligna de vías biliares frecuentemente requieren drenaje pero no puede ser llevado a cabo por CPRE. Las punciones percutáneas han mostrado ser útiles pero con múltiples complicaciones hasta en el 30% de los casos. Con el advenimiento del Ultrasonido Endoscópico (USE) el drenaje guiado por este método se ha reportado en diversas ocasiones. El equipo y recursos humanos para llevar a cabo dicho procedimiento no están disponibles en todos los países. Nosotros reportamos nuestra experiencia inicial del drenaje de la vía biliar por punción transgástrica o transduodenal guiada por USE. El éxito técnico y clínico fue alto y nos posicionamos como uno de los pocos grupos a nivel mundial, y el único en el país, que lleva a cabo este procedimiento.

**Citas a este artículo: 4**


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# Vascular Invasion in Pancreatic Cancer

## *Predictive Values for Endoscopic Ultrasound and CT Imaging*

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**Objectives:** To evaluate the accuracy of endoscopic ultrasound (EUS) to determine vascular invasion in patients with pancreatic cancer.

**Methods:** Data were obtained prospectively from patients with a pancreatic lesion who underwent EUS, computed tomographic (CT) imaging, and surgery from March 2005 to March 2010.

**Results:** Fifty patients were included with a mean ± SD age 61 ± 11.5 years; 27 (54%) were women. The sensitivity, specificity, positive predictive value, and negative predictive value for EUS were the following: 61.1 (95% CI, 38.6–79.7), 90.3 (95% CI, 75.1-96.7), 78.6 (95% CI, 52.4–92.4), and 80 (95% CI, 64.1–90), respectively. The area under the curve for EUS and that for CT were 0.80 (95% CI, 0.68–0.92) and 0.74 (95% CI, 0.61–0.86), respectively. The positive predictive value for arterial invasion was 100% (95% CI, 61–100) for EUS and 60% (95% CI, 31.3–83.2) for CT. There were no complications associated with the EUS or the CT.

**Conclusion:** Endoscopic US is a very good option to detect vascular invasion in patients with pancreatic cancer and is especially sensitive for arterial invasion. When it is available, we recommend that it be performed in addition to CT staging.

**Key Words:** endoscopic ultrasound, pancreatic cancer, vascular invasion

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Endoscopic ultrasound (EUS) is emerging as one of the most accurate diagnostic tests to evaluate pancreatic cancers.[1,2] Most patients with pancreatic adenocarcinoma present with either metastatic or locally advanced disease. The 5-year survival rates after pancreatic adenocarcinoma resection have been reported to be 17% to 25%.[3,4] It is therefore important to identify patients who are most likely to benefit from surgical resection.[5,6] In addition to metastatic disease, vascular invasion is considered to preclude surgical resection[7] and is a predictor for poor prognosis. It is also the most important predictor for poor prognosis after local resection.[8] However, new surgical options are emerging in cases when venous invasion is present.[9] The aim of this study was to evaluate the accuracy of EUS to determine vascular invasion in patients with pancreatic cancer.

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## MATERIALS AND METHODS

We reviewed data obtained prospectively from patients with clinical, biochemical, or/and radiological diagnosis (US and computed tomography [CT]) of a pancreatic lesion who underwent EUS in the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ) from March 2005 to March 2010. There were 152 procedures in patients with pancreatic cancer, 102 patients were excluded because they did not undergo surgery to yield a pathological specimen to confirm the imaging results. Before each procedure, complete blood cell count, INR, and prothrombin time were obtained for all patients to minimize the risk of bleeding. An experienced endoscopist in EUS (M.A.R.L.) performed the EUS in all cases. Written informed consent was obtained from each patient, and the procedures were performed under deep sedation with midazolam, propofol, and fentanyl by an anesthetist. The ultrasound unit was a linear GF UCT-140 echoendoscope (Olympus, American Corp, Melville, NY) with an Aloka console SSD 5500. It was used with an 8-cm long 22- or 19-gauge EchoTip needle (Wilson-Cook Medical Inc, Winston-Salem, NC) in cases where fine needle aspiration (FNA) was performed. The tissue samples obtained by EUS-FNA were sent for histological and cytological evaluation.

A 16- or 64-slice multidetector CT (Somatom, Sensation 16 or 64; Siemens, München, Germany) was used in the CT examination, and images were obtained with a section thickness of 3 to 5 mm with a reconstruction interval of 2 to 2.5 mm. All patients received intravenous contrast, 120 mL of Conray (Mallinckrodt Baker Inc, St Louis, Mo) was given 45 seconds before the CT examination. Forty milliliters of ioditrast M60 (Justesa Imagen Mexicana) was diluted in 1000 mL of water and given to all patients orally 1 hour before CT imaging. All CT images were analyzed by at least 2 certified radiologists. All cases were analyzed on a workstation with the capability to produce coronal reformatted images. All CT and endoscopic studies were performed in the same center. Vascular invasion was defined as tumor being contiguous with 75% of the vessel on CT imaging and the "teardrop" sign and morphologic deformation of the vessel at the tumor site.[10–12] In the case of EUS, data considered indicative of vascular invasion were dilated peripancreatic collateral vessels, loss of vascular interface, or observed tumor within the vessel lumen.[13] The final diagnosis (the criterion standard) was made based on the results from the surgical specimen. All patients were hospitalized after the procedure (EUS) for at least 2 hours for surveillance for possible complications.

### Statistical Analyses

Descriptive statistics were used for demographic variables. Results are expressed as mean ± SD or medians and ranges, according to distribution. The diagnostic usefulness of EUS/CT

**TABLE 1.** Computed Tomography for Vascular Invasion (Arteries and Veins) Measured by Sensitivity, Specificity, Positive and Negative Predictive Values, and Likelihood Ratios

| Parameter | EUS, % (95% CI) | CT, % (95% CI) |
|---|---|---|
| Sensitivity | 61.1 (38.6–79.7) | 55.6 (33.7–75.4) |
| Specificity | 90.3 (75.1–96.7) | 93.1 (78–98) |
| Positive predictive value | 78.6 (52.4–92.4) | 83.3 (55.2–95.3) |
| Negative predictive value | 80 (64.1–90) | 77.1 (61–87.9) |
| LR+ | 6.3 (2–19.6) | 8.06 (1.99–32.6) |
| LR− | 0.43 (0.24–0.79) | 0.48 (0.28–0.82) |

LR+ indicates positive likelihood ratio; LR−, negative likelihood ratio.

to determine vascular invasion was evaluated for sensitivity, specificity, predictive values, and likelihood ratios. All statistical analyses were conducted using the statistics program SPSS/PC, version 12.0 (SPSS Inc, Chicago, Ill).

## RESULTS

Fifty patients (27 women [54%]) with a mean ± SD age of age 61 ± 11.5 years were included. The median size for pancreatic lesions was 40 mm (range, 12–70 mm). Adequate tissue samples by EUS were obtained for histological evaluation in 17 (89.4%) of 19 patients; however, tissue sampling was not attempted in 31 patients (62%). Pancreatic tumor location was as follows: head, 41 cases (81%); body, 5 cases (10%); tail, 2 cases (4.25%); and uncinate process, 2 (4.25%). After surgery, histological vascular invasion was demonstrated in 18 patients (36%), vein invasion was shown in 11 (22%), and arterial invasion was shown in 9 (18%).

To assess the diagnostic accuracy of both EUS and CT for vascular invasion, sensitivity, specificity, and positive and negative predictive values were calculated (Table 1). The areas under the curve for EUS and CT were 0.80 (95% CI, 0.68–0.92) and 0.74 (95% CI, 0.61–0.86), respectively (Fig. 1). Table 2 shows these results according to the type of vessel invasion (vein vs artery). In 2 of the 3 patients with false-positive results on EUS, CT was also erroneously reported; whereas in the remaining case, CT was correct. Two (28.5%) of the 7 patients with false-negative readings by EUS had a correct evaluation by CT. There were 2 cases (10.2%) with a false-positive result on CT, and in both of them, EUS assessment was correct. There were 8 patients (16%) with false-negative results by CT and 5 by EUS. No complications related to EUS or CT were observed in our study.

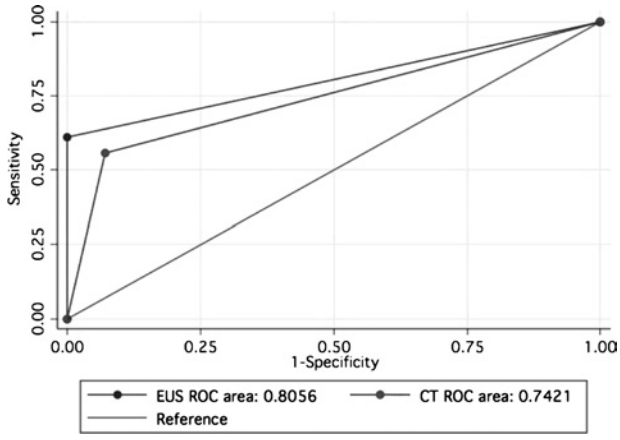


**FIGURE 1.** Area under curve for EUS and CT for diagnostic yield regarding vascular invasion in pancreatic cancer.

**TABLE 2.** Diagnostic Accuracy of EUS and CT Specific for Arteries Measured by Sensitivity, Specificity, Positive and Negative Predictive Values, and Likelihood Ratios

| Parameter | EUS, % (95% CI) | CT, % (95% CI) |
|---|---|---|
| Sensitivity | 66.7 (35–87.9) | 66.7 (35.4–87.9) |
| Specificity | 100 (91.4–100) | 90 (76.9–96) |
| Positive predictive value | 100 (61–100) | 60 (31.3–83.2) |
| Negative predictive value | 93.2 (81.8–97.7) | 92.3 (79.7–97.3) |
| LR+ | — | 6.67 (2.36–18.8) |
| LR− | 0.33 (0.13–0.84) | 0.37 (0.14–0–95) |

## DISCUSSION

In the present work, we observed that EUS is a useful tool to evaluate vascular invasion in patients with pancreatic cancer. According to our data, EUS has better diagnostic yield than CT, especially for diagnosis of arterial invasion. The data from this study are important because they were classified according to type of vessel involved (artery or vein) and the criterion standard used as a reference was the pathological specimen. Correctly predicting vascular invasion in patients with pancreatic cancer is very important because vascular invasion is considered to be a good predictor for prognosis and the most important predictor for poor prognosis after local resection.[8] Until recently, CT was the preferred diagnostic method for vascular invasion. However, the missing rate was high (20%).

In recent years, EUS has shown a good ability to detect vascular invasion but is highly operator dependent. The diagnostic values for sensitivity, specificity, positive likelihood ratios, and negative likelihood ratios ranged between 68.8 and 100, 87.9 and 92.2, 4.6 and 17.9, and 0.2 and 0.5, respectively. According to our data, EUS is a very useful tool for diagnosis or to rule out vascular invasion. For a negative diagnosis, we have an error rate of less than 20%. It is clear that CT has advantages over EUS to detect distant metastases, and because of that, we cannot to dispense with this important study in pancreatic patients. We can consider these 2 imaging modalities as complementary. Conversely, it is well known that EUS allows small neoplasias (<3 cm) to be identified that are not detected by other diagnostic modalities, and it also tissue samples to be obtained for cytologic examination.[14] Puli et al[3] note that the diagnostic accuracy may differ among vessels. Previous data found poor

**TABLE 3.** Diagnostic Accuracy of EUS and CT Specific for Veins Measured by Sensitivity, Specificity, Positive and Negative Predictive Values, and Likelihood Ratios

| Parameter | EUS, % (95% CI) | CT, % (95% CI) |
|---|---|---|
| Sensitivity | 80 (49–94.3) | 30 (11–60) |
| Specificity | 87.5 (73.9–94.5) | 89.7 (76.4–96) |
| Positive predictive value | 61.5 (34–82.3) | 43 (16–75) |
| Negative predictive value | 94.6 (82.3–98.5) | 83.3 (69.4–91–7) |
| LR+ | 6.4 (2.66–15.3) | 2.9 (0.78–11) |
| LR− | 0.23 (0.07–0.8) | 0.78 (0.48–1.26) |

**TABLE 4.** Specific Vessels Affected According to EUS and CT and Definitive Results According to Surgery

| Vessel | EUS N = 14 Patients* (Shared Patients With Surgery) | CT N = 12 Patients* (Shared Patients With Surgery) | Surgery N = 18 Patients* |
|---|---|---|---|
| SMA | 3 (3) | 5 (2) | 6 |
| Celiac trunk | 1 (1) | 1 (1) | 1 |
| Hepatic artery | 2 (2) | 2 (2) | 2 |
| Splenic artery | 2 (0) | 0 (1) | 0 |
| SMV | 8 (5) | 5 (3) | 6 |
| Portal vein | 6 (2) | 0 (0) | 4 |
| Splenic vein | 5 (1) | 0 (0) | 1 |

*A particular patient can be affected in more than one vessel.

SMA indicates superior mesenteric artery; SMV, superior mesenteric vein.

accuracy for EUS for evaluation of the superior mesenteric artery. In the present work, EUS shows very superior performance AQ10 to detect arterial invasion compared with CT (positive predictive value of EUS, 100%, vs positive predictive value of CT, 60%; Table 2). This is a very important point. Recently, invasion of veins is no longer considered a contraindication for surgery AQ11 T3 (Table 3), but vascular invasion of arterial vessels still is a con- T4 traindication (Table 4).[15,16] Our findings are in agreement with previous reports that regard EUS as a more accurate modality for local T staging and for predicting vascular invasion, especially in tumors less than 3 cm, whereas helical CT is better for the evaluation of distant metastasis and for staging larger tumors.[17]

In our data, for false-positive results by EUS, there was a change of diagnosis with the CT in 1 patient. In false-negative results by CT, the EUS correctly detected vascular invasion in 3 patients (6%).

Endoscopic US has many benefits over CT, including generally better performance for detecting vascular invasion (with the associated economic and health consequences), and the ability to obtain tissue samples. For this reason, we recommend that all patients with pancreatic cancer be evaluated by EUS regardless of the CT result for vascular invasion.

The main limitation of the present work is the retrospective analysis. Some advantages of our work are the following: the criterion standard that was used, the differentiation of the results among different vessels, and the sample size. Previous studies have used different criterion standards of surgery results. Regarding previous studies that consider surgery as the criterion standard, only 2 studies have similar sample size.[3] The present data are very important for future meta-analysis regarding the diagnostic accuracy between different vessels because data for individual vessel involvements could not be extracted from most of the previous studies.[3]

In conclusion, EUS is a very good option to detect vascular invasion in patients with pancreatic cancer. When it is available, we recommend that it be performed to supplement CT results.

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La decisión de resecabilidad de un cáncer pancreático es un punto sumamente trascendente en la práctica clínica que tradicionalmente se evalúan con tomografía computada (TC). La presencia de metástasis o invasión vascular son los criterios utilizados para esta decisión, siendo este último criterio el más difícil de evaluar. El Ultrasonido endoscópico (USE) es una herramienta que ha mostrado gran utilidad en este grupo de pacientes. En este trabajo comparamos los valores predictivos del USE y de la TC para predecir invasión vascular en pacientes con cáncer de páncreas. Encontramos que el USE es una opción muy buena para predecir invasión vascular con una curva ROC mejor que la documentada por TC.

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