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- 1176** Liver cystic echinococcosis and human host immune and autoimmune follow-up: A review

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- 1190** Safety and efficacy of ledipasvir/sofosbuvir on hepatitis C eradication in hepatitis C virus/human immunodeficiency virus co-infected patients

He X, Hopkins L, Everett G, Carter WM, SchroppDyce C, Abusaada K, Hsu V

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WJH covers topics concerning liver biology/pathology, cirrhosis and its complications, liver fibrosis, liver failure, portal hypertension, hepatitis B and C and inflammatory disorders, steatohepatitis and metabolic liver disease, hepatocellular carcinoma, biliary tract disease, autoimmune disease, cholestatic and biliary disease, transplantation, genetics, epidemiology, microbiology, molecular and cell biology, nutrition, geriatric and pediatric hepatology, diagnosis and screening, endoscopy, imaging, and advanced technology. Priority publication will be given to articles concerning diagnosis and treatment of hepatology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJH*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

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Current concepts and future strategies in the antimicrobial therapy of emerging Gram-positive spontaneous bacterial peritonitis

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Abstract

Spontaneous bacterial peritonitis (SBP) is the most common infection in end-stage liver disease patients. SBP is defined as an ascitic fluid infection with a polymorphonuclear leucocyte count $\geq 250/\text{mm}^3$ without an evident intra-abdominal surgically treatable source. Several mechanisms contribute to SBP occurrence, including translocation of gut bacteria and their products, reduced intestinal motility provoking bacterial overgrowth, alteration of the gut's barrier function and local immune responses. Historically, Gram-negative enteric bacteria have been the main causative agents of SBP, thereby guiding the empirical therapeutic choice. However, over the last decade, a worryingly increasing prevalence of Gram-positive and multi-drug resistant (MDR) SBP has been seen. Recently, the microbiological spectrum of SBP seems to have changed in Europe due to a high prevalence of Gram-positive bacteria (48%-62%). The overall proportion of MDR bacteria is up to 22%-73% of cases. Consequently, empirical therapy based on third-generation cephalosporins or amoxicillin/clavulanic acid, can no longer be considered the standard of care, as these drugs are associated with poor outcomes. The

aim of this review is to describe, with an epidemiological focus, the evidence behind this rise in Gram-positive and MDR SBP from 2000 to present, and illustrate potential targeted therapeutic strategies. An appropriate treatment protocol should include daptomycin plus ceftaroline and meropenem, with prompt stepdown to a narrower spectrum when cultures and sensitivity data are available in order to reduce both cost and potential antibiotic resistance development.

Key words: Spontaneous bacterial peritonitis; Multi-drug resistant bacteria; End-stage liver disease; Cirrhosis; Critically ill patient

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Core tip: Spontaneous bacterial peritonitis (SBP) is the most common infection in end-stage liver disease cirrhotic patients. Over the last decade, a worryingly increasing prevalence of Gram-positive and multi-drug resistant (MDR) SBP causative bacteria has been seen. Numerous driving factors have been proposed as associated with this epidemiological change. The aim of this review is to describe, with an epidemiological focus, the evidence behind this rise in Gram-positive and MDR SBP from 2000 to present, and illustrate potential targeted therapeutic strategies. Third-generation cephalosporins should be avoided in clinical settings with a high prevalence of MDR. An appropriate treatment protocol should include daptomycin plus ceftaroline and meropenem.

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INTRODUCTION

The development of abdominal ascites is the most frequent complication in cirrhotic patients^[1], and infected ascites, better known as spontaneous bacterial peritonitis (SBP), is the most common infection in these patients, together with urinary tract infections^[2]. SBP is defined as a polymorphonuclear (PMN) leucocyte count $\geq 250/\text{mm}^3$, with or without positive ascitic culture and the absence of other sources of sepsis in the peritoneum or adjacent tissues^[3]. SBP is a distinct clinical entity, as opposed to bacteriascites (positive ascitic culture with PMN $< 250/\text{mm}^3$, not needing therapy in cases of no accompanying symptoms) and secondary bacterial peritonitis, which are usually polymicrobial and linked to the inflammation or perforation of an abdominal organ^[3].

Several mechanisms contribute to the occurrence of SBP, including translocation of gut bacteria and their

products, reduction of intestinal motility provoking bacterial overgrowth, alteration of the gut's barrier function and local immune responses^[4]. These premises explain why historically Gram-negative bacteria (GNB) have been the main causative agents of SBP, thereby guiding the empirical therapeutic choice^[5]. However, over the last decade the prevalence of Gram-positive bacteria (GPB) and multidrug resistant (MDR) SBP has increased worryingly^[6]. Important driving factors for this epidemiological change have been the extensive use of quinolones, as a prophylactic measure, and the increasing degree of instrumentalization of patients suffering from cirrhosis^[7]. Consequently, empirical therapy based on third-generation cephalosporins (3GCs) or amoxicillin/clavulanic acid, especially within a healthcare setting, can no longer be considered the standard of care due to poor outcomes^[8].

Bacterial infections are the primary cause of death in patients with end-stage liver disease (ESLD), and require timely and appropriate treatment^[9]. Thus, the aim of this review is to describe, with an epidemiological focus, the evidence behind this rise in Gram-positive and MDR SBP from 2000 to present, and illustrate potential targeted therapeutic strategies.

EPIDEMIOLOGY OF SBP: CHANGE OF PARADIGM

Globally, since 2000, there has been an increasing relevance of the role of GPB with respect to SBP (Figure 1). A description of this change follows, according to a geographical criterion.

Asia

Before 2000, GNB were, in consistency with the previous literature^[10], the most prevalent etiologic cause of SBP in Asian cohorts of SBP patients. Then, changes occurred, but in a distinct fashion from country to country. In a retrospective study conducted in South Korea, which reviewed records of individuals diagnosed with SBP in 1995, 1998 and 1999, the rate of GPB was just 18.6% (44/237), with just 5 cases of infection by *Staphylococcus aureus* and 3 by *Enterococcus* spp., while the majority of GPB were represented by *Streptococcus* spp.^[11]. These data were substantially confirmed by another South Korean retrospective study (episodes referring to the period from October 1998 to August 2003) that showed a proportion of GPB equal to 20.8% (22/106); no strains of *S. aureus* were detected, but there were 16 streptococci and 8 enterococci^[12].

In a further South Korean retrospective study, which analysed cases from January 2002 to December 2004, the prevalence of GPB was also low; the bacterial isolates totalled 204 and *S. aureus*, *Enterococcus* spp. and *Streptococcus* spp. accounted for 3.9% (8/204), 3.9% (8/204) and 8.8% (18/204), respectively^[13]. In addition, Heo *et al*^[14] found a marginal proportion of GPB in their South Korean retrospective cohort (from June 2005



Figure 1 Worldwide prevalence of spontaneous bacterial peritonitis due to Gram-positive bacteria.

to May 2006), namely 16.7% (11/65). Interestingly, when keeping South Korean retrospective cohorts under consideration, the rate of GPB increases when data are split according to the onset of infection. Cheong *et al.*^[15] reviewing medical records from 1 January 2000 to 30 June 2007, found a relatively low number of GPB (22.9%, 54/236), but among nosocomial SBP (N-SBP; which occurred > 48 h after hospital admission), this rate was equal to 29.3% (37/126). At any rate, South Korea does not seem to be impacted by a remarkable increment of GPB. A recently published retrospective study, referring to a 10-year period (from 2005 to 2014) and comparing cases of culture-positive SBP with cases of culture-negative SBP, showed a rate of GPB equal to 25.5 (66/259), with a low number of *S. aureus* (2.7%, 7/259) and *Enterococcus* spp. (3.5%, 9/259)^[16].

On the contrary, in China, the epidemiological shift towards GPB has been more apparent. In a retrospective study of 98 patients, 48 from 1996 to 2002, and 50 from 2003 to 2009, the proportion of GPB passed from 27% (13/48) to 53% (26/49); the rate of staphylococci also increased from 14% (7/48) to 37% (18/49), but with only 1 case of methicillin-resistant *S. aureus* (MRSA)^[17]. More importantly, in-hospital mortality was greater among GPB-SBP than GNB-SBP cases (26% vs 11%, namely 7 deaths vs 2 deaths), although the result was not significant ($P = 0.20$)^[17]. In a subsequent retrospective study conducted in China, which reviewed medical records from 2011 to 2013, Li *et al.*^[18] found a less prominent rate of GPB, equal to 27.8% (85/306), overlapping between nosocomial (27.3%, 27/99) and non-nosocomial episodes (28.0%, 58/207). Nonetheless,

a worrisome percentage of MRSA stood out from this study: 37.5% (6/16) among non-nosocomial infections and, even worse, 85.7% (6/7) among nosocomial cases^[18].

More recently in a Chinese study, performed to compare the microbiological profiles of N-SBP and community acquired SBP (CA-SBP), 575 strains were isolated from January 2014 to December 2014. In the CA-SBP cases, the most frequently isolated pathogens were *Escherichia coli* (*E. coli*) (27.4%), coagulase-negative staphylococci (22%), *Klebsiella pneumoniae* (13.7%), *Enterococcus* spp. (9%) and *Streptococcus* (8.2%). In the N-SBP, the most frequently isolated pathogens were *E. coli* (25.9%), coagulase-negative staphylococci (23.4%), *K. pneumoniae* (2.5%), *Enterococcus* spp. (16.6%) and *Streptococcus* (6.2%). In the statistical analysis, there were no significant differences in the distributions of GPB between the CA and N-SBP. In contrast, compared with the CA-SBP, the distribution of enterococci was increased in the N-SBP (9.0% vs 16.6%, $P < 0.05$)^[19].

Different results have come from studies in other Asian countries. In Iran, a prospective study (from November 2005 to December 2007) showed a proportion of GPB equal to 27.3% (12/44)^[20]. A similar result (28.6%, 90/314) was found in another study conducted in Iran (from April 2005 to September 2011)^[21]. A small cohort from Pakistan showed a relatively low percentage of GPB: 25% (3/12) in a 2007 prevalence study^[22].

Africa

In an Egyptian prospective cohort, the burden of GPB turned out to be as high as 73.2%, namely 30

out of 41 episodes, including 10 cases by *Listeria monocytogenes*^[23]. In contrast, a retrospective study conducted in Nigeria, which reviewed medical records from August 2009 to July 2010, showed a much smaller proportion of GPB, which although not marginal was equal to 31.8% (7/22)^[24].

South America

In a Brazilian retrospective study referring to a 5-year period (from November 2001 to November 2006), a significant rate of GPB emerged despite the lack of a complete microbiological profile of 63 cases [*Streptococcus* spp. 23.8% (15/63), *S. aureus* 7.9% (5/63)]^[25]. A more recent and prospective multicentre study conducted in Argentina, from March 2011 to April 2012, showed a clear predominance of GPB over GNB [21/33 (63.6%)]; of note, the study, which aimed at investigating the potential association between proton pump inhibitors (PPIs) and SPB, showed no significant difference with regard to PPIs' consumption and duration between patients with and without SBP (as well as with and without other infections) nor with regard to the type of bacteria^[26].

North America

A high number of GPB was found in a United States retrospective study, referring to medical records from July 2009 and November 2010: 80% (8/10), including two vancomycin-resistant enterococci (VRE)^[27]. The high impact of GPB in SBP in North America has been further confirmed in a Canadian retrospective cohort that reviewed cases from February 2003 to May 2011; the data indicated that 57.1% (44/77) and 34.1% of these strains (15/44) were resistant to 3GCs (acquired or intrinsic resistance)^[28].

Europe

In a prospective French study conducted from January 1996 to March 2001, GPB accounted for 68.3% (125/183) of ascitic fluid infections^[29]. GPB cases were mainly explained by enterococci (43/125), streptococci (43/125) and *S. aureus* (36/125); the large majority of the latter (94.4%, 34/36) were MRSA^[29]. In that study, the multivariate analysis showed that an infection provoked by *S. aureus* (while taking into account cases of bacteraemia) was independently linked to a higher mortality rate in cirrhotic patients (OR = 2.845, 95%CI: 1.421-5.695, $P = 0.031$)^[29]. In France, Gram-positive cocci are today the predominant ascitic fluid microbes, with isolates ranging from 47.4%^[30] to 56.1% of cases^[31]. Data from a Spanish study, conducted from April 1998 to April 2000, demonstrated a low proportion of GPB (20.3%, 11/54)^[32].

In a retrospective study by Ariza *et al.*^[33], reviewing medical records related to a subsequent period from 2001 to 2009, GPB rate was again relevant [35.8% (88/246)]. Surprisingly, the lowest percentage was among nosocomial infections (27.3%, 18/66) in comparison with community-acquired (36.5%, 18/85) and healthcare-related infections (41.1%, 39/95); however, the highest rate of MDR-GPB

was found among nosocomial cases (27.8%, 5/18)^[33]. In Italy, interesting data stem from a recently published randomized clinical trial (RCT), conducted from 2011 to 2014. The aim of that RCT was to compare ceftazidime to the combination of daptomycin plus meropenem, applied as an empirical treatment of N-SBP (in this case, defined if it occurred > 72 h after hospital admission); in particular, 62.5% (10/16) of culture-positive cases were due to GPB (8 enterococci)^[34]. Of note, the broad-spectrum regimen proved to be significantly more effective with regard to the primary outcome, namely the resolution of SBP after 7 d of treatment (86.7% vs 25%; $P < 0.001$); that finding did not come as a surprise, in the light of the total rate of MDR bacteria [37.5% (6/16)]^[34].

In Germany, the growing number of GPB was already a touted issue, more than a decade ago. In a prospective cohort from 2002 to August 2006, Umgelter *et al.*^[35] found a GPB rate equal to 45.4% (20/44, 10 *E. faecium*). Again, in Germany, a retrospective cohort covering a 12-year period (from January 2001 to November 2011) found a predominance of GPB (53.7%, 65/121), where *Enterococcus* spp. (28 out of 65 GPB) played a highly relevant role^[36]. In the multivariate analysis, use of antibiotics (OR = 3.875, 95%CI: 1.189-12.631, $P = 0.025$) and nosocomial infection (OR = 3.287, 95%CI: 1.311-8.243, $P = 0.011$) were the independent predictors of enterococcal infections, which were associated with higher mortality (12% probability of 90-d survival vs 50% in non-enterococcal cases, $P = 0.022$ by log-rank test) in case of treatment with a 3GC or a quinolone^[36]. Also, in a more recent German prospective cohort, followed from March 2012 to February 2016, and focusing only on nosocomial and healthcare-related SBP, GPB were relevant [*Staphylococcus* spp., *Enterococcus* spp. and *Streptococcus* spp. accounted for 40% of cases (20/50)]^[37].

Greece was one the first countries to warn about the increasing importance of GPB-SBP. Cholongitas *et al.*^[38], in a retrospective evaluation, observed that the rate of GPB went from 25% (5/20) to 59.1% (13/22%) in two subsequent periods of time, from 1998 to 1999 and from 2000 to 2002, respectively. This trend in Greece was confirmed by another retrospective study, including cases from 2008 to May 2011, with 26 episodes out of 47 (55%) due to GPB, most of all streptococci (10 isolates), followed by 6 *E. faecalis*, 3 *E. faecium* and 2 *S. aureus*; neither VRE nor MRSA were detected^[6].

In Denmark, a retrospective review of medical records from 2000 to 2006 showed a proportion of Gram-positive cocci, without considering other GPB, equal to 45.9% (86/187)^[39].

CONTROVERSIES RELATED TO THE DIAGNOSIS OF SBP BY GRAM-POSITIVE BACTERIA

Although some authors have previously considered the isolation of coagulase-negative staphylococci within ascitic

culture as skin contamination^[15,40,41], today the clinical significance of such a finding appears relevant in both nosocomial^[19,34] and community acquired infections^[19]. More than 40 years ago, MacGregor and Beaty^[42] proposed guidelines to differentiate contamination from significant positive blood cultures in bacteraemic patients; nowadays guidelines, however, are still lacking in their ability to differentiate contamination from significant positive ascitic cultures.

In our opinion, the absence of recommendations based on solid evidence does not justify concluding isolation of coagulase-negative staphylococci as contamination^[15]. Future studies are required to establish the hypothetical difference between the contaminants or pathogens.

CURRENT THERAPEUTIC STRATEGIES FOR SBP BY GPB

The current guidelines rely on outdated epidemiology^[43-45] and take into account neither the increasing prevalence of GPB nor the emerging phenomenon of MDR bacteria as aetiological agents of SBP^[46]. Opinion leaders recommend 3GCs^[47] or piperacillin/tazobactam, meropenem ± glycopeptide^[1] for patients at risk of MDR SBP. The role of piperacillin/tazobactam in the treatment of life-threatening infections due to extended spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* is a controversial issue^[47-49]; moreover, meropenem is active against ESBL-producing *Enterobacteriaceae* but is weakly active against Gram-positive cocci^[50,51]. Glycopeptides are active against Gram-positive cocci, as well as MDR, but their use is not advisable because of their nephrotoxicity. Acute kidney injury is higher in ESLD patients, it could be related to hemodynamic instability and/or hepatorenal syndrome^[52]. Furthermore, the minimum inhibitory concentration (MIC) of vancomycin appears to be shifting upwards in some institutions, a phenomenon known as MIC creep; and, where the MIC increase occurs, treatment failure is common^[53,54]. Teicoplanin MIC creep has also been described; but, regardless, when it is administered intravenously it does not achieve therapeutic concentration in the ascitic fluid^[55].

Antibiotics active against VRE are linezolid, tigecycline, and daptomycin. Linezolid is not recommended in the majority of ESLD and SBP patients because of high frequency thrombocytopenia^[56]. A tigecycline dose adjustment is requested in patients with severe hepatic impairment^[57,58]. Daptomycin is a lipopeptide active against MDR GPB, including drug-resistant and drug-susceptible *S. aureus* and VRE^[59]. Decreased susceptibility to daptomycin has been reported in drug-resistant *S. aureus*; it is frequently accompanied by a paradoxical decrease in beta-lactam resistance, a process known as the "see-saw" effect. Despite the observed discordance in resistance phenotypes, the combination of daptomycin/beta-lactams has been proven clinically effective for the prevention and treatment of infections due to daptomycin-resistant *S. aureus* strains^[60,61]. Therefore, daptomycin monotherapy

should not be used for the treatment of SBP due to MRSA, unless the isolate is likely to be fully susceptible^[62]. The combination of daptomycin plus ceftaroline is highly active against MRSA, the potent bactericidal activity appears to be sufficiently robust to allow rapid de-escalation to single ceftaroline with daptomycin sparing^[63]. Furthermore, ceftaroline in combination with daptomycin restores daptomycin activity against daptomycin-resistant VRE strains^[64]. Aminoglycoside antibiotics, especially gentamicin, are used in combination with ampicillin for the treatment of enterococcal systemic infections^[65]. Despite rigorous patient monitoring, nephrotoxicity appears in 10%-25% of therapeutic courses^[66]. Therefore, their use is not advisable in cirrhotic patients. In recent years, an alternative treatment with ampicillin plus ceftriaxone has proved to be safer than gentamicin in combination with ampicillin^[67]. In ESLD patients, the combination of ampicillin plus ceftriaxone should be used for SBP due to enterococci, regardless of aminoglycoside resistance-level status.

FUTURE PERSPECTIVES

The 20th century has been characterized by the dramatic effect of the large-scale use of antibiotics after their discovery, saving millions of lives^[68]. Unfortunately, natural selection and misuse of antibiotics, both in human beings and in animals, have led to the development of difficult-to-treat infections by MDR bacteria, also known as superbugs, the nightmare of the new century^[69]. Research efforts by pharmaceutical companies are not keeping pace with the worldwide spread of superbugs and this has prompted new strategies to optimize existing resources, such as the reviving of old antibiotics^[70], the implementation of antimicrobial stewardship programs^[71,72], and the judicious use of new anti-infective agents^[73]. However, the epidemiology of bacterial infections has a huge inter-centre variability and the therapeutic approach should be inspired by the principle of "one size does not fit all", which obviously also applies to SBP^[74]. In other words, the current challenge is to accurately identify patients with SBP for whom empirical broad-spectrum therapy would be appropriate, with special attention to MDR-GPB in contexts where their prevalence is relevant^[74].

Some risk factors are well established. The setting of acquisition (nosocomial or healthcare-related vs community-acquired) and the history of exposition to antibiotics, such as beta-lactams and/or quinolones, are probably the main ones^[75,76]. Exposure to quinolones, largely used to prevent SBP in cirrhotic patients, is a significant risk factor for MRSA infections^[77,78]. Moreover, antibiotics administered within the past 30 d before SBP diagnosis and a lower sepsis-related organ failure assessment (commonly known as SOFA) score proved to be significantly associated with SBP by GPB in a cohort of 77 patients^[79]. The impact of MDR-GPB on SBP patient mortality is not well investigated; recently, we performed a systematic review aimed at summarizing the evidence from the literature concerning

Table 1 Characteristics of the studies

Ref.	Journal	Publication year	Observation time span	Study design	Country, clinical setting	Proportion of infections by GPB (%)
Asia - South Korea						
Park <i>et al</i> ^[11]	<i>J Gastroenterol Hepatol</i>	2003	1995, 1998, 1999	RC, single centre	South Korea, University Hospital	44/237 (18.6)
Song <i>et al</i> ^[12]	<i>J Korean Med Sci</i>	2006	1998 (October) - 2003 (August)	RC, single centre	South Korea, University Hospital	22/106 (20.8)
Cho <i>et al</i> ^[13]	<i>Scand J Infect Dis</i>	2007	2002-2004	RC, single centre	South Korea, University Hospital	34/204 (16.6)
Heo <i>et al</i> ^[14]	<i>Gut Liver</i>	2009	1998 (June) - 2003 (May)	RC, multicentre	South Korea	11/65 (16.7)
Cheong <i>et al</i> ^[15]	<i>Clin Infect Dis</i>	2009	2000 (January) - 2007 (June)	RC, single centre	South Korea, University Hospital	54/236 (22.9)
Na <i>et al</i> ^[16]	<i>Scand J Infect Dis</i>	2017	2005-2014	RC, single centre	South Korea, University Hospital	66/259 (25.5)
Asia - China						
Gou <i>et al</i> ^[17]	<i>Saudi Med J</i>	2010	1996-2009	RC, single centre	China, University Hospital	39/97 (42.2)
Li <i>et al</i> ^[18]	<i>World J Gastroenterol</i>	2015	2011-2013	RC, single centre	China, University Hospital	85/306 (27.8)
Shi <i>et al</i> ^[19]	<i>Sci Rep</i>	2017	2014	RC, single centre	China, Tertiary Hospital	293/575 (50.9)
Asia - Other countries						
Kamani <i>et al</i> ^[20]	<i>BMC Gastroenterol</i>	2008	2005 (November) - 2007 (December)	PC, single centre	Iran, University Hospital	12/44 (27.3)
Sheikhabaei <i>et al</i> ^[21]	<i>Int J Hepatol</i>	2014	2005 (April) - 2011 (September)	PC, single centre	Iran, University Hospital	90/314 (28.6)
Zaman <i>et al</i> ^[22]	<i>J Ayub Med Coll Abbottabad</i>	2011	2007	PC, single centre	Pakistan, University Hospital	3/12 (25)
Africa						
El Sayed Zaki <i>et al</i> ^[23]	<i>J Infect Public Health</i>	2011	Not provided	PC, single centre	Egypt, University Hospital	30/41 (73.2)
Oladimeji <i>et al</i> ^[24]	<i>Pan Afr Med J</i>	2013	2009 (August) - 2010 (July)	RC, single centre	Nigeria, University Hospital	7/22 (31.8)
South America						
Reginato <i>et al</i> ^[25]	<i>Sao Paulo Med J</i>	2011	2001 (November) - 2006 (November)	RC, single centre	Brazil, Tertiary Hospital	20/63 (31.7)
Terg <i>et al</i> ^[26]	<i>J Hepatol</i>	2015	2011 (March) - 2012 (April)	PC, multicentre	Argentina	21/33 (63.6)
North America						
Tandon <i>et al</i> ^[27]	<i>Clin Gastroenterol Hepatol</i>	2012	2009 (July) - 2010 (November)	RC, single centre	United States, University Hospital	8/10 (80)
Chaulk <i>et al</i> ^[28]	<i>Can J Gastroenterol Hepatol</i>	2014	2003 (February) - 2010 (May)	RC, single centre	Canada, Tertiary Hospital	44/77 (57.1)
Europe						
Campillo <i>et al</i> ^[29]	<i>Clin Infect Dis</i>	2002	1996 (January) - 2001 (March)	PC, single centre	France, Tertiary Hospital	125/183 (68.3)
Piroth <i>et al</i> ^[31]	<i>BMC Infect Dis</i>	2014	2010-2011	PC, multicentre	France, University Hospitals	32/57 (56.1)
Thévenot <i>et al</i> ^[30]	<i>Am J Gastroenterol</i>	2016	2014 (March) - 2015 (August)	PC, multicentre	France	40/84 (47.4)
Fernández <i>et al</i> ^[32]	<i>Hepatology</i>	2002	1998 (April) - 2000 (April)	PC, single centre	Spain, University Hospital	11/54 (20.3)
Ariza <i>et al</i> ^[33]	<i>J Hepatol</i>	2012	2001-2009	RC, single centre	Spain, University Hospital	88/246 (35.8)
Piano <i>et al</i> ^[34]	<i>Hepatology</i>	2016	2011-2014	RCT, multicentre	Italy	10/16 (62.5)
Umgelter <i>et al</i> ^[35]	<i>Infection</i>	2009	2002 (January) - 2006 (August)	PC, single centre	Germany, University Hospital	20/44 (45.4)
Reuken <i>et al</i> ^[36]	<i>Aliment Pharmacol Ther</i>	2009	2002 (January) - 2011 (November)	RC, single centre	Germany, Tertiary Hospital	65/121 (53.7)
Lutz <i>et al</i> ^[37]	<i>Eur J Clin Invest</i>	2017	2012 (March) - 2016 (February)	PC, single centre	Germany, University Hospital	20/50 (40)
Cholongitas <i>et al</i> ^[38]	<i>Liver Int</i>	2005	1998-200	RC, single centre	Greece, University Hospital	18/42 (42.9)
Novovic <i>et al</i> ^[39]	<i>Scand J Gastroenterol</i>	2012	2000-2006	RC, multicentre	Denmark, University Hospitals	86/187 (45.9)

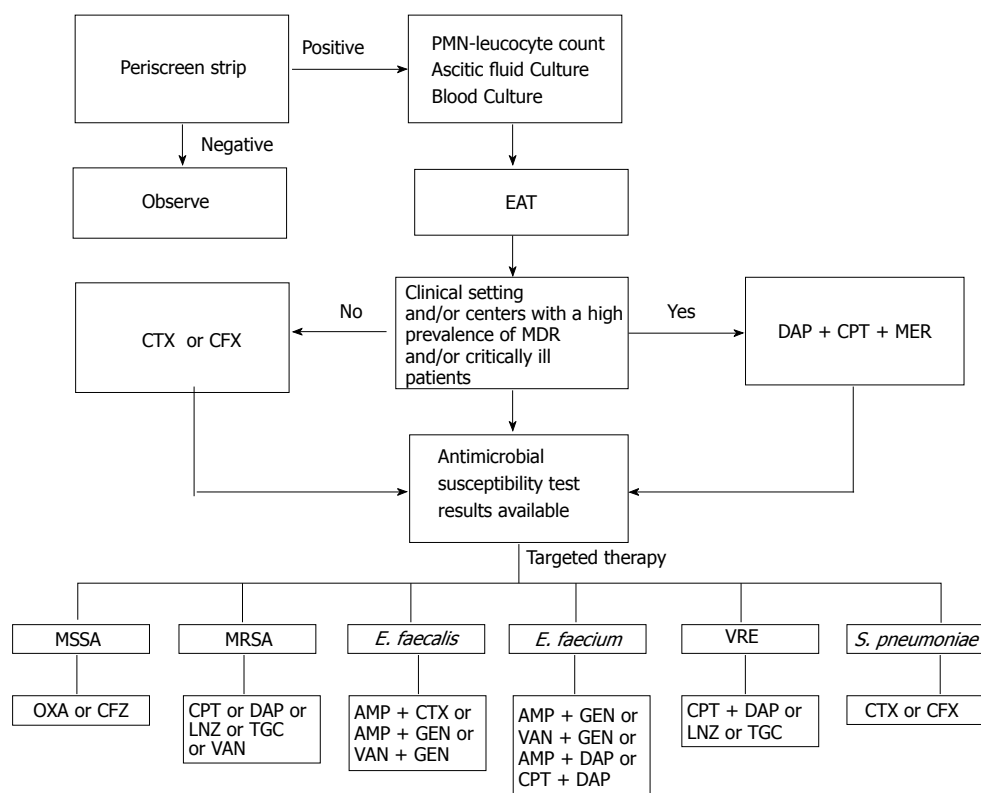


Figure 2 Infection management algorithm of spontaneous peritonitis due to Gram-positive bacteria^[45,46,51,54,61,62,65,72,80,82-84]. AMP: Ampicillin; CFZ: Cefotaxime; CFZ: Cefazolin; CPT: Ceftaroline; CTX: Ceftriaxone; DAP: Daptomycin; EAT: Empiric antibacterial therapy; GEN: Gentamicin; LNZ: Linezolid; MDR: Multidrug resistant; MER: Meropenem; MRSA: Methicillin-resistant *S. aureus*; MSSA: Methicillin-susceptible *S. aureus*; OXA: Oxacillin; PMN: Polymorphonuclear; TGC: Tigecycline; VAN: Vancomycin; VRE: Vancomycin-resistant enterococci.

the epidemiology of nosocomial cases of SBP, in order to highlight the importance of MDR bacteria outcome; of the initial 2556 manuscripts retrieved, only 9 were included in the qualitative analysis, and a quantitative analysis on mortality was not possible^[80].

Risk factors could be integrated into predictive models of mortality in individuals with SBP so as to further help identify patients in need of more aggressive therapeutic strategies from the very start of the infective process^[81].

CONCLUSION

GPB are increasingly important as causative agents of SBP. In some contexts, they even supersede GNB as the main cause of this infection (Table 1 describes the main features of included studies). In parallel with this phenomenon, physicians have to face the rise of superbugs, both among GNBs and GPBs. In presence of particularly worrisome epidemiological data and other risk factors for superbug infections, a broad-spectrum empirical approach is required, encompassing antibiotics with well-established activity against pathogens, such as MRSA and VRE, pending the results of microbiological tests that would allow a de-escalation strategy whenever possible.

On the basis of the current literature, we propose a treatment algorithm for SBP due to GPB (Figure 2). If an ESLD patient with ascites is "symptomatic" for

SBP (temperature above 38 °C or below 36.5 °C, chills, abdominal tenderness, arterial hypotension, developing or worsening hepatic encephalopathy, gastrointestinal bleeding within the previous 15 d) it is necessary to perform a Periscreen strip on the ascitic fluid^[30]. If the Periscreen strip is positive the patient requires immediate hospitalization with comparison of this result with cytology and immediate microbiological cultures. A culture of ascitic fluid and blood should systematically be carried out at the bedside^[34]. Empiric antibacterial therapy (EAT) should be initiated after obtaining appropriate cultures. 3GCs should not be used in clinical settings and/or centres with a high prevalence of MDR bacteria. ESLD patients with SBP in clinical settings and/or centres with a high prevalence of VRE, MRSA and ESBL should immediately receive broad-spectrum EAT^[82]. An appropriate treatment protocol should include daptomycin plus ceftaroline and meropenem^[83]. When the culture is positive and susceptibility data are available, an antibiotic with a narrower spectrum should be promptly initiated (early de-escalation strategy); this strategy limits the selection of antibiotic resistances and saves on costs^[83].

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REFERENCES

- 1 Solà E, Solé C, Ginès P. Management of uninfected and infected ascites in cirrhosis. *Liver Int* 2016; **36** Suppl 1: 109-115 [PMID: 26725907 DOI: 10.1111/liv.13015]
- 2 Jalan R, Fernandez J, Wiest R, Schnabl B, Moreau R, Angeli P, Stadlbauer V, Gustot T, Bernardi M, Canton R, Albillos A, Lammert F, Wilmer A, Mookerjee R, Vila J, Garcia-Martinez R, Wendon J, Such J, Cordoba J, Sanyal A, Garcia-Tsao G, Arroyo V, Burroughs A, Ginès P. Bacterial infections in cirrhosis: a position statement based on the EASL Special Conference 2013. *J Hepatol* 2014; **60**: 1310-1324 [PMID: 24530646 DOI: 10.1016/j.jhep.2014.01.024]
- 3 Mowat C, Stanley AJ. Review article: spontaneous bacterial peritonitis—diagnosis, treatment and prevention. *Aliment Pharmacol Ther* 2001; **15**: 1851-1859 [PMID: 11736714]
- 4 Pericleous M, Sarnowski A, Moore A, Fijten R, Zaman M. The clinical management of abdominal ascites, spontaneous bacterial peritonitis and hepatorenal syndrome: a review of current guidelines and recommendations. *Eur J Gastroenterol Hepatol* 2016; **28**: e10-e18 [PMID: 26671516 DOI: 10.1097/MEG.0000000000000548]
- 5 Fagiuoli S, Colli A, Bruno R, Burra P, Craxi A, Gaeta GB, Grossi P, Mondelli MU, Puoti M, Sagnelli E, Stefani S, Toniutto P. Management of infections in cirrhotic patients: report of a consensus conference. *Dig Liver Dis* 2014; **46**: 204-212 [PMID: 24021271 DOI: 10.1016/j.dld.2013.07.015]
- 6 Alexopoulou A, Papadopoulos N, Eliopoulos DG, Alexaki A, Tsiriga A, Toutouza M, Pectasides D. Increasing frequency of gram-positive cocci and gram-negative multidrug-resistant bacteria in spontaneous bacterial peritonitis. *Liver Int* 2013; **33**: 975-981 [PMID: 23522099 DOI: 10.1111/liv.12152]
- 7 Acevedo J. Multiresistant bacterial infections in liver cirrhosis: Clinical impact and new empirical antibiotic treatment policies. *World J Hepatol* 2015; **7**: 916-921 [PMID: 25954474 DOI: 10.4254/wjh.v7.i7.916]
- 8 Merli M, Lucidi C, Di Gregorio V, Falcone M, Giannelli V, Lattanzi B, Giusto M, Ceccarelli G, Farcomeni A, Riggio O, Venditti M. The spread of multi drug resistant infections is leading to an increase in the empirical antibiotic treatment failure in cirrhosis: a prospective survey. *PLoS One* 2015; **10**: e0127448 [PMID: 25996499 DOI: 10.1371/journal.pone.0127448]
- 9 Fernández J, Gustot T. Management of bacterial infections in cirrhosis. *J Hepatol* 2012; **56** Suppl 1: S1-12 [PMID: 22300459 DOI: 10.1016/S0168-8278(12)60002-6]
- 10 Garcia-Tsao G. Spontaneous bacterial peritonitis. *Gastroenterol Clin North Am* 1992; **21**: 257-275 [PMID: 1568776]
- 11 Park YH, Lee HC, Song HG, Jung S, Ryu SH, Shin JW, Chung YH, Lee YS, Suh DJ. Recent increase in antibiotic-resistant microorganisms in patients with spontaneous bacterial peritonitis adversely affects the clinical outcome in Korea. *J Gastroenterol Hepatol* 2003; **18**: 927-933 [PMID: 12859722]
- 12 Song JY, Jung SJ, Park CW, Sohn JW, Kim WJ, Kim MJ, Cheong HJ. Prognostic significance of infection acquisition sites in spontaneous bacterial peritonitis: nosocomial versus community acquired. *J Korean Med Sci* 2006; **21**: 666-671 [PMID: 16891810 DOI: 10.3346/jkms.2006.21.4.666]
- 13 Cho JH, Park KH, Kim SH, Bang JH, Park WB, Kim HB, Kim NJ, Oh MD, Lee HS, Choe KW. Bacteremia is a prognostic factor for poor outcome in spontaneous bacterial peritonitis. *Scand J Infect Dis* 2007; **39**: 697-702 [PMID: 17654346 DOI: 10.1080/00365540701299582]
- 14 Heo J, Seo YS, Yim HJ, Hahn T, Park SH, Ahn SH, Park JY, Park JY, Kim MY, Park SK, Cho M, Um SH, Han KH, Kim HS, Baik SK, Kim BI, Cho SH. Clinical features and prognosis of spontaneous bacterial peritonitis in Korean patients with liver cirrhosis: a multicenter retrospective study. *Gut Liver* 2009; **3**: 197-204 [PMID: 20431746 DOI: 10.5009/gnl.2009.3.3.197]
- 15 Cheong HS, Kang CI, Lee JA, Moon SY, Joung MK, Chung DR, Koh KC, Lee NY, Song JH, Peck KR. Clinical significance and outcome of nosocomial acquisition of spontaneous bacterial peritonitis in patients with liver cirrhosis. *Clin Infect Dis* 2009; **48**: 1230-1236 [PMID: 19302016 DOI: 10.1086/59758]
- 16 Na SH, Kim EJ, Nam EY, Song KH, Choe PG, Park WB, Bang JH, Kim ES, Park SW, Kim HB, Oh MD, Kim NJ. Comparison of clinical characteristics and outcomes of spontaneous bacterial peritonitis and culture negative neutrocytic ascites. *Scand J Gastroenterol* 2017; **52**: 199-203 [PMID: 27797274 DOI: 10.1080/00365521.2016.1245776]
- 17 Gou YZ, Liu B, Pan L, Yu HT, Wang JP, Wang DC. Pathogens of spontaneous bacterial peritonitis change in northern China. *Saudi Med J* 2010; **31**: 1152-1156 [PMID: 20953533]
- 18 Li YT, Yu CB, Huang JR, Qin ZJ, Li LJ. Pathogen profile and drug resistance analysis of spontaneous peritonitis in cirrhotic patients. *World J Gastroenterol* 2015; **21**: 10409-10417 [PMID: 26420967 DOI: 10.3748/wjg.v21.i36.10409]
- 19 Shi L, Wu D, Wei L, Liu S, Zhao P, Tu B, Xie Y, Liu Y, Wang X, Liu L, Zhang X, Xu Z, Wang F, Qin E. Nosocomial and Community-Acquired Spontaneous Bacterial Peritonitis in patients with liver cirrhosis in China: Comparative Microbiology and Therapeutic Implications. *Sci Rep* 2017; **7**: 46025 [PMID: 28382951 DOI: 10.1038/srep46025]
- 20 Kamani L, Mumtaz K, Ahmed US, Ali AW, Jafri W. Outcomes in culture positive and culture negative ascitic fluid infection in patients with viral cirrhosis: cohort study. *BMC Gastroenterol* 2008; **8**: 59 [PMID: 19091136 DOI: 10.1186/1471-230X-8-59]
- 21 Sheikhbahaei S, Abdollahi A, Hafezi-Nejad N, Zare E. Patterns of antimicrobial resistance in the causative organisms of spontaneous bacterial peritonitis: a single centre, six-year experience of 1981 samples. *Int J Hepatol* 2014; **2014**: 917856 [PMID: 24778884 DOI: 10.1155/2014/917856]
- 22 Zaman A, Kareem R, Mahmood R, Hameed K, Khan EM. Frequency of microbial spectrum of spontaneous bacterial peritonitis in established cirrhosis liver. *J Ayub Med Coll Abbottabad* 2011; **23**: 15-17 [PMID: 23472401]
- 23 El Sayed Zaki M, El Shabrawy WO, El-Eshrawy MM, Aly Eletreby S. The high prevalence of *Listeria monocytogenes* peritonitis in cirrhotic patients of an Egyptian Medical Center. *J Infect Public Health* 2011; **4**: 211-216 [PMID: 22000850 DOI: 10.1016/j.jiph.2011.06.002]
- 24 Oladimeji AA, Temi AP, Adekunle AE, Taiwo RH, Ayokunle DS. Prevalence of spontaneous bacterial peritonitis in liver cirrhosis with ascites. *Pan Afr Med J* 2013; **15**: 128 [PMID: 24255734 DOI: 10.11604/pamj.2013.15.128.2702]
- 25 Reginato TJ, Oliveira MJ, Moreira LC, Lamanna A, Acencio MM, Antonangelo L. Characteristics of ascitic fluid from patients with suspected spontaneous bacterial peritonitis in emergency units at a tertiary hospital. *Sao Paulo Med J* 2011; **129**: 315-319 [PMID: 22069130]
- 26 Terg R, Casciato P, Garbe C, Cartier M, Stieben T, Mendizabal M, Niveyro C, Benavides J, Marino M, Colombato L, Barbara D, Silva M, Salgado P, Barreyro F, Fassio E, Gadano A; Study Group of Cirrhosis Complications of the Argentine Association for the Study of Liver Disease. Proton pump inhibitor therapy does not increase the incidence of spontaneous bacterial peritonitis in cirrhosis: a multicenter prospective study. *J Hepatol* 2015; **62**: 1056-1060 [PMID: 25481567 DOI: 10.1016/j.jhep.2014.11.036]
- 27 Tandon P, Delisle A, Topal JE, Garcia-Tsao G. High prevalence of antibiotic-resistant bacterial infections among patients with cirrhosis at a US liver center. *Clin Gastroenterol Hepatol* 2012; **10**: 1291-1298 [PMID: 22902776 DOI: 10.1016/j.cgh.2012.08.017]
- 28 Chaulk J, Carbonneau M, Qamar H, Keough A, Chang HJ, Ma

- M, Kumar D, Tandon P. Third-generation cephalosporin-resistant spontaneous bacterial peritonitis: a single-centre experience and summary of existing studies. *Can J Gastroenterol Hepatol* 2014; **28**: 83-88 [PMID: 24288693]
- 29 **Campillo B**, Richardet JP, Kheo T, Dupeyron C. Nosocomial spontaneous bacterial peritonitis and bacteremia in cirrhotic patients: impact of isolate type on prognosis and characteristics of infection. *Clin Infect Dis* 2002; **35**: 1-10 [PMID: 12060868 DOI: 10.1086/340617]
- 30 **Thévenot T**, Briot C, Macé V, Lison H, Elkrief L, Heurgué-Berlot A, Bureau C, Jézéquel C, Riachi G, Louvet A, Pauwels A, Ollivier-Hourmand I, Anty R, Carbonell N, Labadie H, Aziz K, Grasset D, Nguyen-Khac E, Kaassi M, Hermann S, Tanné F, Mouillot T, Roux O, Le Thuaut A, Cervoni JP, Cadranet JF, Schnee M; CFEHTP, ANGH and the PerDRISLA study group. The Periscreen Strip Is Highly Efficient for the Exclusion of Spontaneous Bacterial Peritonitis in Cirrhotic Outpatients. *Am J Gastroenterol* 2016; **111**: 1402-1409 [PMID: 27619833 DOI: 10.1038/ajg.2016.344]
- 31 **Piroth L**, Pechinot A, Di Martino V, Hansmann Y, Putot A, Patry I, Hadou T, Jaulhac B, Chirouze C, Rabaud C, Lozniewski A, Neuwirth C, Chavanet P, Minello A. Evolving epidemiology and antimicrobial resistance in spontaneous bacterial peritonitis: a two-year observational study. *BMC Infect Dis* 2014; **14**: 287 [PMID: 24884471 DOI: 10.1186/1471-2334-14-287]
- 32 **Fernández J**, Navasa M, Gómez J, Colmenero J, Vila J, Arroyo V, Rodés J. Bacterial infections in cirrhosis: epidemiological changes with invasive procedures and norfloxacin prophylaxis. *Hepatology* 2002; **35**: 140-148 [PMID: 11786970 DOI: 10.1053/jhep.2002.30082]
- 33 **Ariza X**, Castellote J, Lora-Tamayo J, Girbau A, Salord S, Rota R, Ariza J, Xiol X. Risk factors for resistance to ceftriaxone and its impact on mortality in community, healthcare and nosocomial spontaneous bacterial peritonitis. *J Hepatol* 2012; **56**: 825-832 [PMID: 22173153 DOI: 10.1016/j.jhep.2011.11.010]
- 34 **Piano S**, Fasolato S, Salinas F, Romano A, Tonon M, Morando F, Cavallin M, Gola E, Sticca A, Loregian A, Palù G, Zanusi G, Senzolo M, Burra P, Cillo U, Angeli P. The empirical antibiotic treatment of nosocomial spontaneous bacterial peritonitis: Results of a randomized, controlled clinical trial. *Hepatology* 2016; **63**: 1299-1309 [PMID: 26084406 DOI: 10.1002/hep.27941]
- 35 **Umgeleter A**, Reindl W, Miedaner M, Schmid RM, Huber W. Failure of current antibiotic first-line regimens and mortality in hospitalized patients with spontaneous bacterial peritonitis. *Infection* 2009; **37**: 2-8 [PMID: 19169633 DOI: 10.1007/s15010-008-8060-9]
- 36 **Reuken PA**, Pletz MW, Baier M, Pfister W, Stallmach A, Bruns T. Emergence of spontaneous bacterial peritonitis due to enterococci - risk factors and outcome in a 12-year retrospective study. *Aliment Pharmacol Ther* 2012; **35**: 1199-1208 [PMID: 22449290 DOI: 10.1111/j.1365-2036.2012.05076.x]
- 37 **Lutz P**, Nischalke HD, Krämer B, Goeser F, Kaczmarek DJ, Schlabe S, Parcina M, Nattermann J, Hoerauf A, Strassburg CP, Spengler U. Antibiotic resistance in healthcare-related and nosocomial spontaneous bacterial peritonitis. *Eur J Clin Invest* 2017; **47**: 44-52 [PMID: 27861767 DOI: 10.1111/eci.12701]
- 38 **Cholongitas E**, Papatheodoridis GV, Lahanas A, Xanthaki A, Kontou-Kastellanou C, Archimandritis AJ. Increasing frequency of Gram-positive bacteria in spontaneous bacterial peritonitis. *Liver Int* 2005; **25**: 57-61 [PMID: 15698399 DOI: 10.1111/j.14783231.2004.0985.x]
- 39 **Novovic S**, Semb S, Olsen H, Moser C, Knudsen JD, Homann C. First-line treatment with cephalosporins in spontaneous bacterial peritonitis provides poor antibiotic coverage. *Scand J Gastroenterol* 2012; **47**: 212-216 [PMID: 22191479 DOI: 10.3109/00365521.2011.645502]
- 40 **Sewell CM**, Clarridge JE, Young EJ, Guthrie RK. Clinical significance of coagulase-negative staphylococci. *J Clin Microbiol* 1982; **16**: 236-239 [PMID: 7119097]
- 41 **Kim SU**, Chon YE, Lee CK, Park JY, Kim DY, Han KH, Chon CY, Kim S, Jung KS, Ahn SH. Spontaneous bacterial peritonitis in patients with hepatitis B virus-related liver cirrhosis: community-acquired versus nosocomial. *Yonsei Med J* 2012; **53**: 328-336 [PMID: 22318820 DOI: 10.3349/ymj.2012.53.2.328]
- 42 **MacGregor RR**, Beaty HN. Evaluation of positive blood cultures. Guidelines for early differentiation of contaminated from valid positive cultures. *Arch Intern Med* 1972; **130**: 84-87 [PMID: 4556417]
- 43 **European Association for the Study of the Liver**. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. *J Hepatol* 2010; **53**: 397-417 [PMID: 20633946 DOI: 10.1016/j.jhep.2010.05.004]
- 44 **Runyon BA**; AASLD. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. *Hepatology* 2013; **57**: 1651-1653 [PMID: 23463403 DOI: 10.1002/hep.26359]
- 45 **Esposito S**, Leone S, Carosi G. Analysis of current guidelines for intra-abdominal infections. *J Chemother* 2009; **21** Suppl 1: 30-35 [PMID: 19622448 DOI: 10.1179/joc.2009.21.Supplement-1.30]
- 46 **Fiore M**. Letter: the emergence of multi-drug resistant spontaneous bacterial peritonitis: a new challenge for the hepatologist? *Aliment Pharmacol Ther* 2016; **43**: 944-945 [PMID: 27241936 DOI: 10.1111/apt.13539]
- 47 **Dever JB**, Sheikh MY. Review article: spontaneous bacterial peritonitis--bacteriology, diagnosis, treatment, risk factors and prevention. *Aliment Pharmacol Ther* 2015; **41**: 1116-1131 [PMID: 25819304 DOI: 10.1111/apt.13172]
- 48 **Tamma PD**, Rodriguez-Bano J. The Use of Noncarbapenem β -Lactams for the Treatment of Extended-Spectrum β -Lactamase Infections. *Clin Infect Dis* 2017; **64**: 972-980 [PMID: 28362938 DOI: 10.1093/cid/cix034]
- 49 **Retamar P**, López-Cerero L, Muniain MA, Pascual Á, Rodríguez-Baño J; ESBL-REIPI/GEIH Group. Impact of the MIC of piperacillin-tazobactam on the outcome of patients with bacteremia due to extended-spectrum- β -lactamase-producing *Escherichia coli*. *Antimicrob Agents Chemother* 2013; **57**: 3402-3404 [PMID: 23612190 DOI: 10.1128/AAC.00135-13]
- 50 **Edwards JR**. Meropenem: a microbiological overview. *J Antimicrob Chemother* 1995; **36** Suppl A: 1-17 [PMID: 8543486]
- 51 **Leone S**, Bisi L, Rossi M, Gori A. Comment on "Management of infections in cirrhotic patients: report of a consensus conference" S Fagioli et al. [Dig liver dis 2014;46:204-212]. *Dig Liver Dis* 2014; **46**: 573-574 [PMID: 24618097 DOI: 10.1016/j.dld.2014.01.155]
- 52 **Pazhayattil GS**, Shirali AC. Drug-induced impairment of renal function. *Int J Nephrol Renovasc Dis* 2014; **7**: 457-468 [PMID: 25540591 DOI: 10.2147/IJNRD.S39747]
- 53 **Gould IM**. Treatment of bacteraemia: meticillin-resistant *Staphylococcus aureus* (MRSA) to vancomycin-resistant *S. aureus* (VRSA). *Int J Antimicrob Agents* 2013; **42** Suppl: S17-S21 [PMID: 23664580 DOI: 10.1016/j.ijantimicag.2013.04.006]
- 54 **Ippolito G**, Leone S, Lauria FN, Nicastri E, Wenzel RP. Methicillin-resistant *Staphylococcus aureus*: the superbug. *Int J Infect Dis* 2010; **14** Suppl 4: S7-11 [PMID: 20851011 DOI: 10.1016/j.ijid.2010.05.003]
- 55 **Stamatiadis D**, Papaioannou MG, Giamarellos-Bourboulis EJ, Marinaki S, Giamarellou H, Stathakis CP. Pharmacokinetics of teicoplanin in patients undergoing continuous ambulatory peritoneal dialysis. *Perit Dial Int* 2003; **23**: 127-131 [PMID: 12713078]
- 56 **Zhang YM**, Yu W, Zhou N, Li JZ, Xu LC, Xie ZY, Lu YF, Li LJ. High frequency of thrombocytopenia in patients with acute-on-chronic liver failure treated with linezolid. *Hepatobiliary Pancreat Dis Int* 2015; **14**: 287-292 [PMID: 26063030]
- 57 **Leone S**, Rossi M, Bisi L, Gori A, Esposito S. Letter: antibiotic dose adjustment in patients with advanced liver disease. *Aliment Pharmacol Ther* 2013; **38**: 561-562 [PMID: 23937471 DOI: 10.1111/apt.12411]
- 58 **Noviello S**, Ianniello F, Leone S, Fiore M, Esposito S. In vitro activity of tigecycline: MICs, MBCs, time-kill curves and post-antibiotic effect. *J Chemother* 2008; **20**: 577-580 [PMID: 19028619 DOI: 10.1179/joc.2008.20.5.577]
- 59 **Eisenstein BI**, Oleson FB Jr, Baltz RH. Daptomycin: from the mountain to the clinic, with essential help from Francis Tally, MD. *Clin Infect Dis* 2010; **50** Suppl 1: S10-S15 [PMID: 20067387 DOI: 10.1086/647938]
- 60 **Renzone A**, Kelley WL, Rosato RR, Martinez MP, Roch M, Fatouraei

- M, Haeusser DP, Margolin W, Fenn S, Turner RD, Foster SJ, Rosato AE. Molecular Bases Determining Daptomycin Resistance-Mediated Resensitization to β -Lactams (Seesaw Effect) in Methicillin-Resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother* 2016; **61**: [PMID: 27795377 DOI: 10.1128/AAC.01634-16]
- 61 Leone S, Noviello S, Boccia G, De Caro F, Esposito S. Methicillin-resistant *Staphylococcus aureus* infections: role of daptomycin/ β -lactams combination. *Infez Med* 2015; **23**: 99-104 [PMID: 26110289]
- 62 Fiore M, Andreana L. The Possible Role of Anti-Methicillin-Resistant *Staphylococcus Aureus* Antimicrobial Agents in Spontaneous Bacterial Peritonitis. *Infect Dis Rep* 2015; **7**: 6286 [PMID: 26753087 DOI: 10.4081/idr.2015.6286]
- 63 Barber KE, Werth BJ, Rybak MJ. The combination of ceftaroline plus daptomycin allows for therapeutic de-escalation and daptomycin sparing against MRSA. *J Antimicrob Chemother* 2015; **70**: 505-509 [PMID: 25246437 DOI: 10.1093/jac/dku378]
- 64 Sakoulas G, Rose W, Nonejuie P, Olson J, Pogliano J, Humphries R, Nizet V. Ceftaroline restores daptomycin activity against daptomycin-nonsusceptible vancomycin-resistant *Enterococcus faecium*. *Antimicrob Agents Chemother* 2014; **58**: 1494-1500 [PMID: 24366742 DOI: 10.1128/AAC.02274-13]
- 65 Leone S, Noviello S, Esposito S. Combination antibiotic therapy for the treatment of infective endocarditis due to enterococci. *Infection* 2016; **44**: 273-281 [PMID: 26324294 DOI: 10.1007/s15010-015-0836-0]
- 66 Lopez-Novoa JM, Quiros Y, Vicente L, Morales AI, Lopez-Hernandez FJ. New insights into the mechanism of aminoglycoside nephrotoxicity: an integrative point of view. *Kidney Int* 2011; **79**: 33-45 [PMID: 20861826 DOI: 10.1038/ki.2010.337]
- 67 Pericas JM, Cervera C, del Rio A, Moreno A, Garcia de la Maria C, Almela M, Falces C, Ninot S, Castañeda X, Armero Y, Soy D, Gatell JM, Marco F, Mestres CA, Miro JM; Hospital Clinic Endocarditis Study Group. Changes in the treatment of *Enterococcus faecalis* infective endocarditis in Spain in the last 15 years: from ampicillin plus gentamicin to ampicillin plus ceftriaxone. *Clin Microbiol Infect* 2014; **20**: O1075-O1083 [PMID: 25040215 DOI: 10.1111/1469-0691.12756]
- 68 Fauci AS. Infectious diseases: considerations for the 21st century. *Clin Infect Dis* 2001; **32**: 675-685 [PMID: 11229834 DOI: 10.1086/319235]
- 69 Arias CA, Murray BE. Antibiotic-resistant bugs in the 21st century—a clinical super-challenge. *N Engl J Med* 2009; **360**: 439-443 [PMID: 19179312 DOI: 10.1056/NEJMp0804651]
- 70 Theuretzbacher U, Van Bambeke F, Cantón R, Giske CG, Mouton JW, Nation RL, Paul M, Turnidge JD, Kahlmeter G. Reviving old antibiotics. *J Antimicrob Chemother* 2015; **70**: 2177-2181 [PMID: 26063727 DOI: 10.1093/jac/dkv157]
- 71 Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, Srinivasan A, Dellit TH, Falck-Ytter YT, Fishman NO, Hamilton CW, Jenkins TC, Lipsett PA, Malani PN, May LS, Moran GJ, Neuhauser MM, Newland JG, Ohl CA, Samore MH, Seo SK, Trivedi KK. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. *Clin Infect Dis* 2016; **62**: e51-e77 [PMID: 27080992 DOI: 10.1093/cid/ciw118]
- 72 Leone S, Stefani S, Venditti M, Grossi P, Colizza S, De Gasperi A, Scaglione F, Sganga G, Esposito S; Italian Intra-abdominal Infections Working Group. Intra-abdominal infections: model of antibiotic stewardship in an era with limited antimicrobial options. *Int J Antimicrob Agents* 2011; **38**: 271-272 [PMID: 21782394 DOI: 10.1016/j.ijantimicag.2011.06.003]
- 73 Gentile I, Maraolo AE, Borgia G. What is the role of the new β -lactam/ β -lactamase inhibitors ceftolozane/tazobactam and ceftazidime/avibactam? *Expert Rev Anti Infect Ther* 2016; **14**: 875-878 [PMID: 27599088 DOI: 10.1080/14787210.2016.1233060]
- 74 Ison MG. Empiric treatment of nosocomial spontaneous bacterial peritonitis: One size does not fit all. *Hepatology* 2016; **63**: 1083-1085 [PMID: 26836032 DOI: 10.1002/hep.28476]
- 75 Fernandez J, Arroyo V. Bacterial Infections in Cirrhosis: A Growing Problem with Significant Implications. *Clin Liver Dis* 2013; **2**: 102-105 [DOI: 10.1002/cld.169]
- 76 Esposito S, Capuano A, Noviello S, Mazzeo F, Ianniello F, Filippelli A, Rossi F, Leone S. Modification of patients' endogenous bacterial flora during hospitalization in a large teaching hospital in Naples. *J Chemother* 2003; **15**: 568-573 [PMID: 14998082 DOI: 10.1179/joc.2003.15.6.568]
- 77 Weber SG, Gold HS, Hooper DC, Karchmer AW, Carmeli Y. Fluoroquinolones and the risk for methicillin-resistant *Staphylococcus aureus* in hospitalized patients. *Emerg Infect Dis* 2003; **9**: 1415-1422 [PMID: 14718085 DOI: 10.3201/eid0911.030284]
- 78 Couderc C, Jolivet S, Thiébaud AC, Ligier C, Remy L, Alvarez AS, Lawrence C, Salomon J, Hermann JL, Guillemot D; Antibiotic Use and *Staphylococcus aureus* Resistant to Antibiotics (ASAR) Study Group. Fluoroquinolone use is a risk factor for methicillin-resistant *Staphylococcus aureus* acquisition in long-term care facilities: a nested case-case-control study. *Clin Infect Dis* 2014; **59**: 206-215 [PMID: 24729496 DOI: 10.1093/cid/ciu236]
- 79 Kim JH, Jeon YD, Jung IY, Ahn MY, Ahn HW, Ahn JY, Ku NS, Han SH, Choi JY, Ahn SH, Song YG, Han KH, Kim JM. Predictive Factors of Spontaneous Bacterial Peritonitis Caused by Gram-Positive Bacteria in Patients With Cirrhosis. *Medicine (Baltimore)* 2016; **95**: e3489 [PMID: 27124049 DOI: 10.1097/MD.0000000000003489]
- 80 Fiore M, Maraolo AE, Gentile I, Borgia G, Leone S, Sansone P, Passavanti MB, Aurilio C, Pace MC. Nosocomial spontaneous bacterial peritonitis antibiotic treatment in the era of multi-drug resistance pathogens: A systematic review. *World J Gastroenterol* 2017; **23**: 4654-4660 [PMID: 28740354 DOI: 10.3748/wjg.v23.i25.4654]
- 81 Poca M, Alvarado-Tapias E, Concepción M, Pérez-Cameo C, Cañete N, Gich I, Romero C, Casas M, Román E, Castells L, Vargas V, Carrión JA, Guarner C, Soriano G. Predictive model of mortality in patients with spontaneous bacterial peritonitis. *Aliment Pharmacol Ther* 2016; **44**: 629-637 [PMID: 27464682 DOI: 10.1111/apt.13745]
- 82 Fiore M, Andreana L, Leone S. Treatment of spontaneous bacterial peritonitis: beyond the current international guidelines. *Liver Int* 2016; **36**: 918 [PMID: 26750744 DOI: 10.1111/liv.13047]
- 83 Fiore M. Spontaneous bacterial peritonitis due to multidrug resistant bacteria: are the current guidelines outdated? *Eur J Gastroenterol Hepatol* 2016; **28**: 731 [PMID: 27111388 DOI: 10.1097/MEG.0000000000000599]
- 84 Fiore M. Nosocomial spontaneous bacterial peritonitis: discussing a specific infection treatment algorithm. *Liver Int* 2016; **36**: 1074-1075 [PMID: 26787136 DOI: 10.1111/liv.13072]

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Liver cystic echinococcosis and human host immune and autoimmune follow-up: A review

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Abstract

Cystic echinococcosis (CE) is an infectious disease caused by the larvae of parasite *Echinococcus granulosus* (*E. granulosus*). To successfully establish an infection, parasite release some substances and molecules that can modulate host immune functions, stimulating a strong anti-inflammatory reaction to carry favor to host and to reserve self-survival in the host. The literature was reviewed using MEDLINE, and an open access search for immunology of hydatidosis was performed. Accumulating data from animal experiments and human studies provided us with exciting insights into the mechanisms involved that affect all parts of immunity. In this review we used the existing scientific data and discuss how these findings assisted with a better understanding of the immunology of *E. granulosus* infection in man. The aim of this study is to point the several facts that challenge immune and autoimmune responses to protect *E. granulosus* from elimination and to minimize host severe pathology. Understanding the immune mechanisms of *E. granulosus* infection in an intermediate human host will provide, we believe, a more useful treatment with immunomodulating molecules and possibly better protection from parasitic infections. Besides that, the diagnosis of CE has improved due to the application of a new molecular tool for parasite identification by using of new recombinant antigens and immunogenic peptides. More studies for the better understanding of the mechanisms of parasite immune evasion is necessary. It will enable a novel approach in protection, detection and improving of the host inflammatory responses. In contrast, according to the "hygiene hypothesis", clinical applications that decrease the incidence of infection in developed countries and recently in developing countries are at the origin of the increasing incidence of both allergic

and autoimmune diseases. Thus, an understanding of the immune mechanisms of *E. granulosus* infection is extremely important.

Key words: Lymphocytes; Dendritic cells; Immunity; Autoimmunity; Cytokines; *Echinococcus granulosus*

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Core tip: The most common location of a hydatid echinococcal cyst is in the liver. The survival of *Echinococcus* within host tissues, despite the development of specific antibodies, is possible due to specific immunomodulation induced by parasites. Perpetual survival of parasites indicating multi-level systematic evasion against host protective reaction to persist their growth and spreading. Complement modulation, a metabolic adaptation to the host microenvironment, plentiful thermostable immunogenic antigen B in the cystic fluid, and induction of CD4⁺CD8⁺FOXP3⁺ T cells allows the persistence of the parasites. Parasites influence dendritic cell (DC) maturation and impair activation by toll-like receptor. It seems that DC-parasite interaction is pivotal in triggering and regulating parasite induced immunity.

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INTRODUCTION

The dog tapeworm *Echinococcus granulosus* (*E. granulosus*) is the main challenger of a global parasitic zoonosis cystic echinococcosis (CE) in humans caused by the larvae from the infected dog^[1]. After incidental ingestion the larvae of parasite, the oncosphere/exacanth larvae is releasing from the keratinized embryophore in the stomach and intestine of the intermediate host (herbivores or humans). Embryophores in the intestine of man *via* hook movements penetrate into the small intestine of host. Its life cycle develops in dogs and other canids (wolves, foxes, coyotes, jakals) that harbor the adult tapeworm. The larval metacestode form develops in different organs of the intermediate host^[2]. Hydatid cyst is mainly located in the liver (70%) or lungs (20%), but occasionally they may find their way to other organs (kidney 2%, spleen 2% and brain less than 2%)^[3]. In the intermediate host the eggs cross intestinal wall and develop into larvae. The oncosphere is then carried out *via* portal vein flow into the liver and other organs. There oncospheres undergoes a metamorphosis towards the metacestodes. The metacestodes implant into the organ and grow into cysts, with all characteristic layers: Germinal, outer and laminated (Figure 1)^[4,5]. Organs

may also be reached through the lymphatic system^[6]. Echinococcal cysts is surrounded by pericyst (adventia) from the periparasitic host tissue, which surround the larval endocyst (Figure 1A and B). The endocyst is also composed of a cuticular or laminal acellular outer layer and an inner germinal proliferous, which gives rise in a fertile cyst to root capsules and protoscoleces (PSCs)^[7]. Some cysts may also harbor daughter cysts of variable sizes (arrows in Figure 1C). Cysts also contain developing PSCs, which constitute an infectious agent. PSC is developing into the adult tapeworm if will be ingested by a suitable definitive host (sheep, cattle, goat). Some vesicles adhere to the walls by means of a peduncle or remain free within the hydatid fluid. A large number of these vesicles (endogenous daughter vesicles) and free protoscoleces float in the hydatid fluid, together forming the co-called "hydatid sand". New offspring vesicles in the hydatid fluid play the same role and have the same constitution of the vesicle mother. The hydatid liquid is clean and clear. It contain all secreted molecules from parasite and host, which is very similar even identical to that of the host's serum containing Na, K, Cl, and CO₂, a density between 1.008 and 1.015, and alkaline pH^[8]. Thus, in this way, protoscoleces may develop into either a new cyst or in adult parasite. As the cyst later becomes a successful xenograft in the host, it progressively enlarges until symptoms or complications appear^[9,10]. Therefore, the clinical manifestation of infected humans with *E. granulosus*, could be expressed from asymptomatic infection to severe, potentially fatal disease. The parasite die due to dysfunction of germinal membrane (detached, aging or microrraumatism) but the scolex may transform into vesicle trying to preserve the species^[11].

The survival of *Echinococcus* within the host tissues, despite the development of specific antibodies (Abs), is possibly the result of specific immunomodulation induced by the parasite^[12]. This phenomenon has been the subject of study by many researchers during the last two decades. They aimed to investigate the host responses to the parasite. The final goal of the present study was to review these modifications of the immune and autoimmune responses induced by *E. granulosus*. For better understanding of host-parasite interactions in this review human clinical study used complementary to animal studies. However, although some of the mutual interactions between parasite and human host in infection have been resolved, essence of protective mechanisms of human host are still unclear.

IMMUNE RESPONSE TO *E. GRANULOSUS* INFECTION OF THE HOST

Effects on innate immunity

Almost exclusively within the intermediate host's liver, parasitic metacestode vesicles grow infiltratively, very similar to that of malignant tumor. The host immune system reacts to these formations. But there is no data of granulosis-induced immune suppression in echinococcosis

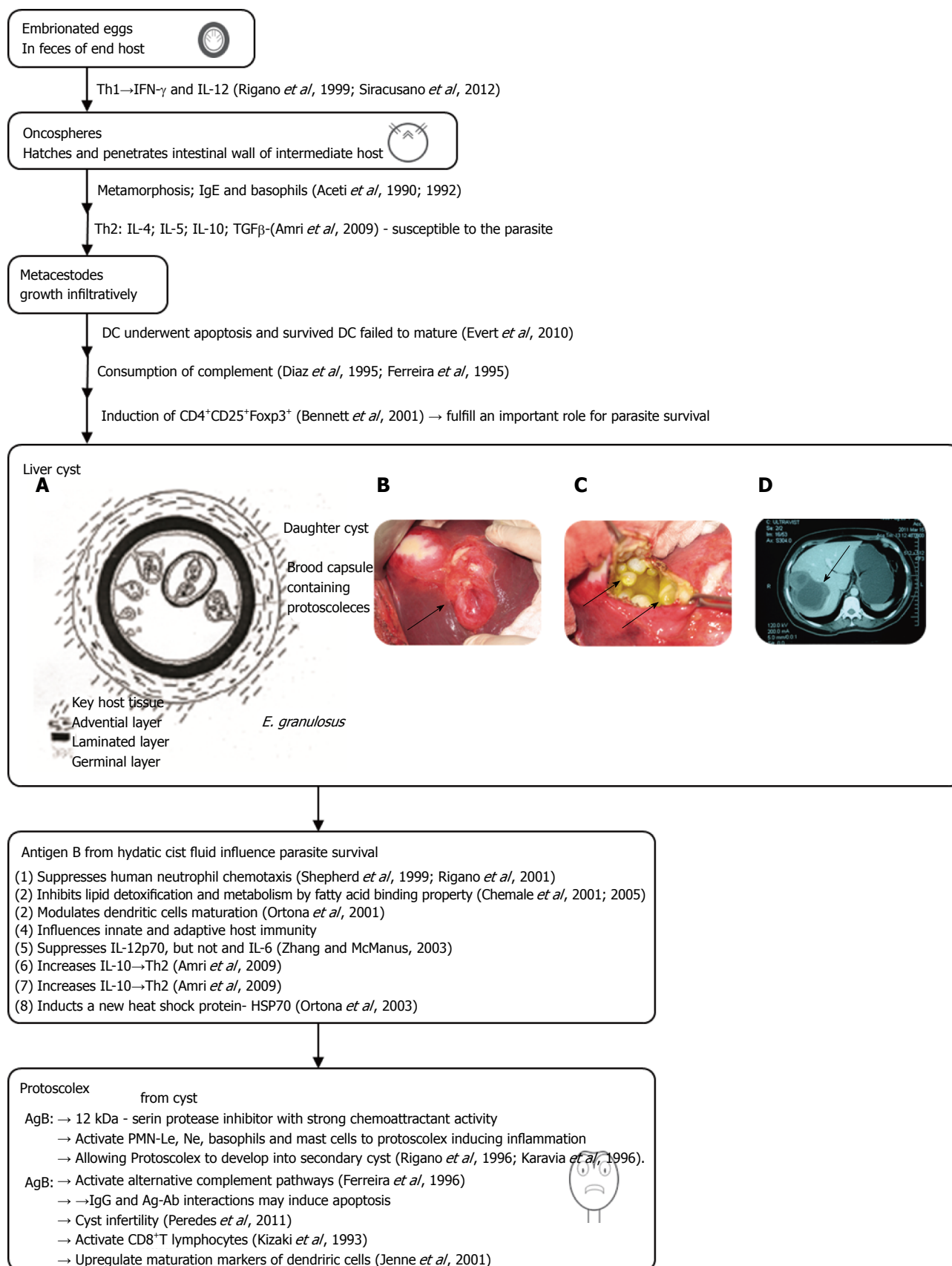


Figure 1 Diagrammatic representation of the development of the *Echinococcus granulosus* liver cyst. A, B: Liver cystic echinococcosis, our surgical material; C: Computed tomography imaging of hepatic cystic echinococcosis; D: Abdominal scan of a female patient with a CE3b cyst in the VI liver segment (adapted from Ref. [120]). IL: Interleukin; IFN: Interferon; TGF: Transforming growth factor; PSC: Protoscolece; PMN: Polymorphonuclear.

on the molecular and cellular level, particularly in the early stages of the infection. On the other hand, there is

no doubt that the defensive immune reaction is missing and parasite survive. Future survival of parasites indicates that they have developed some mechanisms of evasion from host protective immune mechanisms to preserve their expansion^[13]. Many studies in humans and mice showed that after parasite infections at the beginning dominates T helper 1 (Th1) immune responses (Figure 2). Th1 immune responses is characterized by the release of interferon- γ (IFN- γ) and after priming by dendritic cells (DCs) with IL-12^[11,14]. Both are effective in the elimination of the parasite at an early stage. However, it has become clear that the parasite, probably by its excretory/secretory products, actively influences the host immune response, leading it to the Th2 response and parasite survival. Namely, the Th2 cytokine profile of IL-4, IL-5, immunosuppressive IL-10 and transforming growth factor beta (TGF- β) are generally associated with receptive capability of the parasite that leading to progressive disease (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3283565/> - pntd.0001516-Vuitton1)^[15]. On the other hand, the polymorphonuclear (PMN) leukocyte, basophil-mast cell and monocyte participation showed intense local inflammatory reaction to protoscoleces (PSCs)^[16]. Significant increases in the chemiluminescence response, superoxide (O₂) production and phagocyte index have been detected in patients with dead cysts compared with healthy subjects, whereas a marked reduction in all the above markers was observed in patients with liver cysts^[17]. Functionally and metabolically the PMN leukocytes of infected patients are in an activated state^[18]. Regarding basophils, the human basophil degranulation test was found to be positive in 33% of patients with hydatid disease (HD)^[19]. Furthermore, evidence of increased histamine release from hydatid patient basophils following a challenge with anti-human IgE has also been obtained^[20]. It can be concluded that both the generation of histamine releasing factor (HiRF) and production of IgE, which can bind cytokines, may be involved in this stage of infection^[21]. This histamine releasing factor was found to activate basophils through surface-bound IgE, cytokine production and Th2 cell activation^[16,21-23]. Method of antibody-dependent cell-mediated cytotoxicity is well established as an important mechanism by which the host can damage a multicellular parasite, but why it is not happening?

Additionally, it is well known that the surface of many parasitic helminths, including *E. granulosus*, is able to activate the alternative pathway of the complement system^[24,25]. Although the complement can lyse protoscoleces of *E. granulosus*, parasite with some secretion products could be able to consume the complement, which is an ability that has been proposed as the basis of an invasion mechanism by the parasite^[25]. However, the levels of component 3 of complement and chemolytic complement in mice showed no evidence of complement consumption^[25]. Moreover, C3 levels were significantly increased in patients with hydatid disease compared to controls^[16,26]. Thus, it is possible that local consumption at the site of infection may exist, leading to

systemic consumption in the more active cysts. Finally, the existence of several mechanisms of complement modulation was found when comparing complement activation *in vitro* by different *E. granulosus* extracts^[27]. These findings further enhanced the possibility of their significant role in the susceptibility of infection and/or maintenance of the disease.

The parasite must be able to adapt metabolically to the host microenvironment, and antigen B (AgB) could be involved in this process. The thermostable AgB (166 kDa) resists boiling for 15 min without losing antigenicity. Thus, AgB proteins as highly immunogenic acts directly to innate and adaptive immunity. Additionally, many antigen B (AgB) molecules in the hydatid cyst fluid possibly guarantee parasite survival. The gene family of AgB comprising at least 10 unique genes in five subclasses differentially expressed in its life cycle, except EgAgB3 which is expressing predominantly in all cell stages^[28,29]. Because of their fatty acid binding property, some of them are involved in lipid detoxification, transport and metabolism^[30,31]. Also it is well known that its 12 kDa unit is able to inhibit human neutrophil chemotaxis^[32,33]. This unit is a serine protease inhibitor with strong chemoattractant activity. This is a reason for released protoscoleces to develop into secondary cysts^[10]. Co-incubated with *Echinococcus* primary cells, AgB functioning similar to invading oncosphere or metacestode vesicles. In these conditions, some dendritic cells (DCs) dead, and the survived fail to mature^[34]. But, DCs exposed to protoscoleces up-regulated maturation markers and stay functional. Pre-incubation with primary cells and metacestode vesicles, impaired ability of DCs to be activated by the Toll-like receptor ligand LPS. This was not observed in those pre-treated with protoscoleces excretory/secretory products^[35]. The induction of CD4⁺CD25⁺Foxp3⁺ T cells to metacestode E/S-products suggests that these cells play important role for parasite survival. The immunomodulatory products from parasites are therefore of high interest for understanding by infections induced immune pathology and treatment of allergy.

E. GRANULOSUS EVASION MECHANISMS IN THE HOST

Characterization of molecules involved in evasion

In intermediate hosts, protoscoleces develop exclusively in fertile cysts. This formation also consists all of three membranes (inner cellular, other glycin rich and laminated acellular)^[36]. Nevertheless, *E. granulosus* cystic form can induce IgG that is able to cross the tegument and plasma membranes between laminar and germinal layers of the cyst. On the other side, method of antibody-dependent cell-mediated cytotoxicity is well established as an important mechanism by which the host can damage a multicellular parasite. There IgG recognize specific cystic antigens, and antigen-antibody complex may inhibit proliferative process of protoscoleces, but why it is not happening? Due to germinal layer of the cyst is a barrier

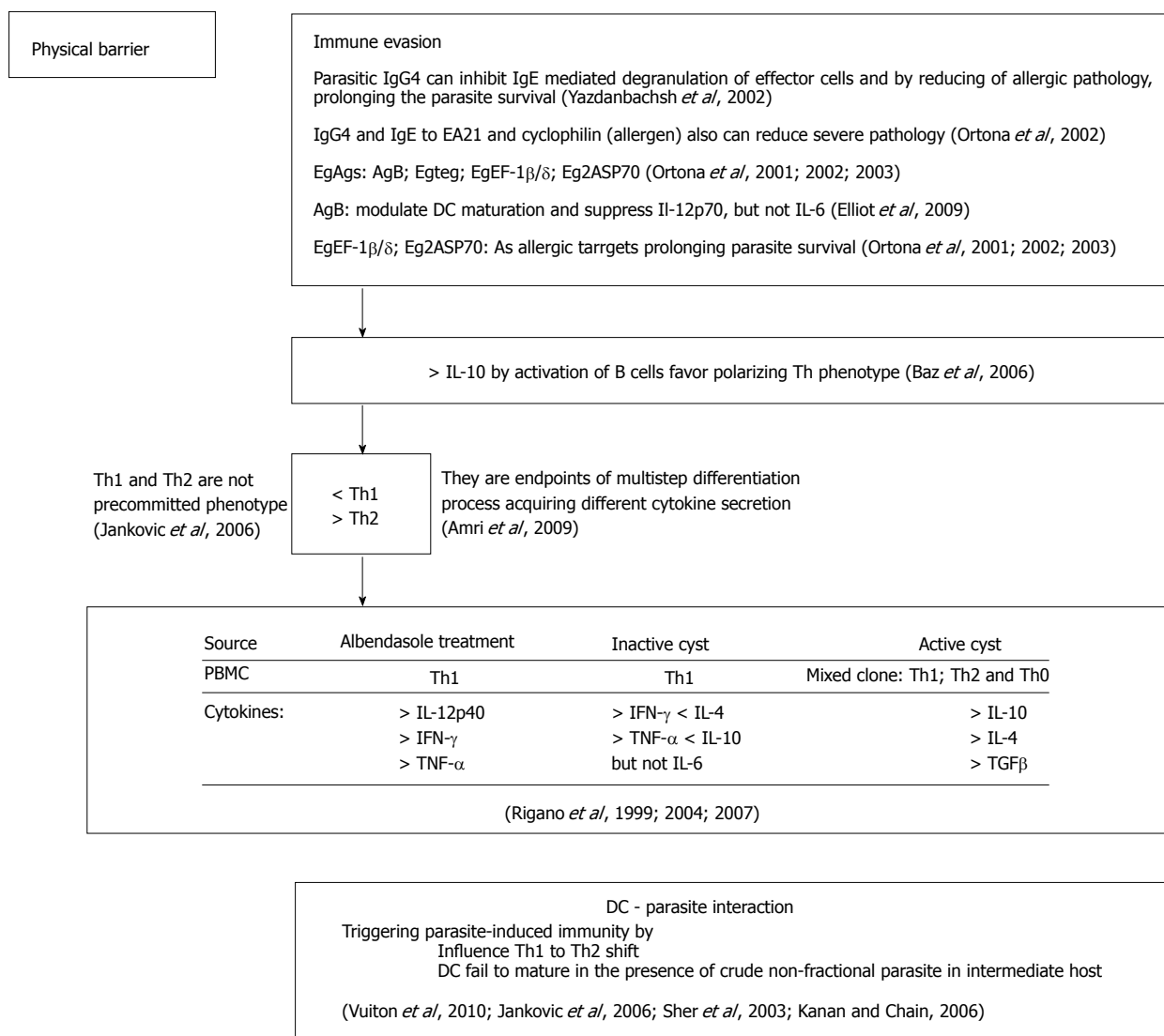


Figure 2 Subversive strategies of *Echinococcus granulosus*. DC: Dendritic cell; IL: Interleukin; IFN: Interferon; TGF: Transforming growth factor.

for immune competent cells of the host^[36]. Except this the parasite evolving other immune evasion strategies^[37]. *E. granulosus* using two main mechanisms to undermine the host immune response: First is passive escape, in which during the development of hydatid cyst, parasites avoids the damaging effects of host immune reaction; and second is immunomodulation, in which the parasite is actively included in the immune reaction to trigger the host's profit^[38,39].

Circulating antibodies as immunological markers in CE

Although patients with hydatidosis releasing amount of circulating IgG, IgM, IgA and IgE antibodies (Abs) to *E. granulosus*, no one is associated with the host protection^[40]. IgG4 in echinococcosis is not able to complement fixation neither is cytophilic, also weakly binding to Fc fragment of immunoglobulins, then is not functional. All of these will support the parasite evasion of host immune response^[41]. Even, parasite-specific IgG4 antibodies by inhibiting IgE mediated degranulation of

effector cells, reducing allergic pathology in the host to prolong parasite survival^[42]. In agreement with this study are findings that significantly lower levels of serum IgG4 antibodies is detected in albendazole-treated patients who exhibited a good therapeutic and clinical response compared to that in poor responders or non-responders. Additionally, data obtained in various countries showed reverse trend of IgG1 levels^[40,42]. Beside that patients showing differences in IgG1 expression. Those without allergic manifestations releasing IgG4 antibodies specific to EA21, whereas patients with allergic manifestations showed IgE specific to the same antigen. Authors have suggested that CE IgG4 obviously work to block pathogenic processes and to, minimize severe pathology in the host providing parasite survival^[42] (Figure 2).

Antigen B and other new antigens in immunomodulation

In CE characterized with Th2 polarized microenvironment, besides AgB, EgTeg and EgEF-1 β/δ , several other parasite molecules can elicit this phenotype. More sophisticated

approach such as proteomic pronounce the presence of a large number of antigenic proteins associated with parasites. Antigen B (AgB) modulates DC maturation and suppresses IL-12p70, but not IL-6 release^[43]. As allergic targets in CE in acute cutaneous allergic manifestation, three conserved constitutive proteins at a molecular level have been identified: EgEF-1 β/δ , EA21 and Eg2ASP70^[44-47]. At least two of three appear to have immune modulatory properties. EgEF-1 β/δ influences immune modulation and is released after the death or degeneration of protoscoleces^[45]. Furthermore, appearance of CD4⁺CD25⁺Foxp3⁺ T cells in excretory/secretory products of metacestode suggests that these cells play important role in survival of parasite in chronic echinococcosis^[35,48]. The secretory and excretory products of parasite helminthes are therefore extremely important for better understanding of immunopathology of parasite infection and for allergy treatment as well. Future immunological studies will give us opportunity to investigate their role and immunomodulatory effects on parasite infections in humans. However, the long- time (years) development of CE highlights the difficulty in understanding the host-parasite relationship^[49,50]. More investigations are necessary for integration of these studies with previous obtained results to recognize and understand well the extreme complexity of the host-parasite interactions. These findings are extremely important for the development and improvement of CE diagnosis and treatment. Finally, it is indispensable for control strategies and vaccine development.

Immunomodulation by cytokine production

Plasticity of both the nature and magnitude of immune host responses depend on infective agents that permit the immune system to tailor its defense strategy. Th1 and Th2 cells are not pre-committed cells with defined phenotype, their phenotype is result of a multistep differentiation process, thus a precursor population acquires secretion of different cytokines profiles^[47]. How *E. granulosus* antigens (Ags) encountering the human immune system can influence the differentiation decision in human echinococcosis? First of all it is well known that the immune response established in *E. granulosus* infection is mainly of Th2-phenotype. Also *E. granulosus* antigens modulate polarized T-cells (Figure 2). Furthermore, increased level of IgG4 and IgE antibodies and induced eosinophilia supporting assertion that the immune response established in *E. granulosus* infection is Th2-dominated. Findings from experimental echinococcosis confirm the hypothesis that early IL-10, secreted by B cells in response to mitogens, may favor parasitic survival by established type-2 cytokine response^[50]. There are many evidence of molecular studies where reciprocity of IL-4/IL-10 is that impairs the Th1 protective response allowing the parasite survival in human host^[51]. In addition, patients responsive to albendazole in peripheral blood monocyte cells (PBMCs) showed high amounts of IFN- γ (Th1-derived), whereas PBMCs from patients who did not respond to albendazol therapy produced a higher level of IL-4 and IL-10 (Th2 derived)^[14].

These findings are in coordination with a molecular studies that detected IL-12p40 mRNA in 86% of successfully albendazole-treated patients at the end of chemotherapy who expressed a high level of IFN- γ and TNF- α DNA^[15,52]. Finally, patient with an inactive cyst expressing Th1 phenotype, while patients with active and transitional cysts showed mixed Th1/Th2 and Th0 phenotype^[53]. No IL-5 and scarce IL-4 and IL-10 is detected in seronegative patients^[54]. Seronegativity occurs due to the host or parasite factors or both preclude the possibility of Th2 cell activation that limiting the production of IL-5, crucial for immunoglobulin expression.

It has been shown recently that bone marrow-derived dendritic cells (DCs) from non-lymphoid tissues show capability for antigen presentation and antigen processing^[55]. Also there are findings that inflammatory mediators or microbial agents promote the migration of DCs into the lymph nodes and other secondary lymphoid organs. By maturation, DCs lose their ability for antigen presentation and gain an increased capability to prime T-cells^[56]. Thus, it is no doubt that DC-parasite interactions are very important for triggering and regulation of parasite-induced immunity. On the other side, *E. granulosus* cystic fluid modulates differentiation and cytokine secretion of dendritic cells^[57]. Finally, these cellular findings established that *E. granulosus* except for modulation of DC maturation is included in the polarization of T lymphocytes toward Th2 phenotype^[58,59].

ADAPTIVE IMMUNITY

Role of dendritic cells in parasite evasion

Dendritic cells (DCs) as an antigen presenting cells, no doubt represent a link between innate and adaptive immune systems. They are inducing immune responses with Th1, Th2 or Th17-dominated phenotype (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3283565/> - pntd.0001516-Everts1)^[60]. After contact with parasite, DCs take up the recognized antigens and undergo maturation in the presence of up regulated MHC/HLA mice/man) complex and co-stimulatory molecules CD86 and CD80^[34,60]. Nevertheless, after migration in the lymph nodes, DCs interact with naïve T cells to promote adaptive immune responses with Th1, Th2, and Th17 cell phenotype (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3283565/> - pntd.0001516-Banchereau1)^[61,62]. There by activation of T regulatory cells, DCs becoming targets for parasite evasion. Mejri *et al*^[63] showed that peritoneal DCs from chronically infected mice, representing the late stage of alveolar echinococcosis. The same authors have reported that DCs in infected mice specifically modulates CD4⁺ and CD8⁺ T cell responses, suggesting their immunosuppressive T regulatory function in echinococcosis^[63]. In intermediate host parasitic larvae migrate from the intestinal entry site to the liver and late metastasis to other organs (lung, kidney, spleen or brain)^[64]. This finding suggest that parasitic larvae encounter DCs *in vivo*^[64]. Despite the general importance of DCs in cellular host-parasite interaction, immunomodulatory molecules that are released by

Echinococcus larvae and have an influence on DC function, are still not characterized. Compared to other helminthic infections, immunomodulatory functions of DCs in *E. granulosus* infection in human host provided less attention, although this is an emerging and important field^[65]. In two reports, Reyes *et al.*^[66] and Terrazas *et al.*^[67] investigated the effects of excretory/secretory products of *Taenia crassiceps cysticerci* on the activation of murine DCs, representing the metacystode larval stage of by *Taenia* infection. DC of susceptible mouse strain when preincubated with parasite excretory/secretory product, authors showed decreased DC maturation because of impaired susceptibility to TLR-dependent stimulus^[66,67]. Whether these interactions are relevant *in vivo* is not clear. First of all due to the spectrum of protein products from metacystode excretion and secretion does not necessary overlap the spectrum of proteins in the hydatid cyst fluid^[68]. For example, AgB is not detected in excreted or secreted products *in vitro* cultivated metacystode vesicles, but this component is well expressed in hydatid cyst fluid^[69]. Second, the intact parasite tissue is showed usually prevents direct contact between hydatid cyst fluid and host immune effector cells. Dendritic cells react with unfractionated helminthic proteins generating anti-parasitic cytotoxic T lymphocyte^[70]. Thus, crude methods of *in vitro* preparation of metacystode antigen, insufficient purified which contain vesicle fluid somatic parasite proteins and contaminating host components, tested concerning their effects on DCs, failed to induce maturation as did a purified mucin-type glycoprotein (Em2) that is usually expressing at the surface of LL-containing metacystode vesicles (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3283565/> - pntd.0001516-Hlsmeier1)^[71,72]. However, it is well known that extrinsically triggered infectious with viruses, bacteria and parasites, usually results in a bystander effect of induced immunosuppression^[73].

Bystander effects of parasite-induced immunosuppression

Dendritic cell apoptosis induction has been reported in nematodes in which their capacity for releasing of pro-inflammatory IL-12 is limited and that prevents activation and proliferation of T cells^[74]. Different from others investigator accept the possibility that the diminished function of DCs in metacystode infection is by induction of apoptosis of immature cells rather than due to inhibition of its maturation. It could be a reason for establishing of an immunosuppressive environment around the parasite lesions. Transforming growth factor beta (TGF- β) signaling is involved very early in this process because in animal evolution they are expressed very early in all invertebrate. Therefore, it is understandable that diminished ability of DCs pre-incubated with excretory/secretory-products of primary cells in metacystode is indirectly mediated by the induction of apoptosis of immature DCs, rather than by direct inhibition of DC maturation. Immature DCs secrete TGF- β , which induces differentiation of naïve T cells into FOXP3⁺ T-regulatory cells, and subsequently immunosuppression around the parasite lesion^[73]. TGF- β signaling is involved very early in animal evolution, thus

TGF like cytokines are expressed very early in many invertebrate, and in parasites as well^[75,76].

Different from DCs incubated with primary cells of metacystode vesicles, those exposed to E/S products of protoscoleces showed up-regulation of surface markers MHC-II and CD86, increased secretion of IL-6, but not IL-10 and impaired ability of DCs to produce IL-12 by toll-like receptor lipopolisaccharides (LPS) stimulated^[74].

Presented phenotypes are similar to that obtained when DCs are incubated with *E. granulosus* hydatid cyst fluid (HCF), and with isolated AgB^[55,59].

In contrast to these investigations, DCs incubated with protoscoleces compounds as presented in their study Rigano *et al.*^[55], 2007 and Kanan and Chain^[59], 2006, dendritic cells did not release elevated levels of IL-10 or IL-12 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3283565/> - pntd.0001516-Kanan1). Presented phenotypes are similar to the obtained when DCs are incubated with *E. granulosus* hydatid cyst fluid (HCF) and with its isolated AgB. It seems that only protoscoleces weakly expressing AgB^[30,77]. Finally, DCs phenotype upon co-incubation with E/S-products of protoscoleces is largely comparable with those incubated with certain *Trypanosoma* antigens, closely associated with the induction of Th2 immune response^[78]. The differences obtained between the responses of DCs to E/S-products of early versus late developmental stages of *E. multilocularis* clearly demonstrates that an induction of tolerance of DCs is not a general characteristic of *Echinococcus* material. It is the results of excretory and secretory repertoire of primary cells. Metacystodes are specifically evolved to carry out these purposes^[79]. The interpretation of obtained results concerning the immune response in echinococcosis by using of *in vitro* co-incubation-systems of *Echinococcus* protoscoleces with host cells^[80-86] or in the mouse model of peritoneal, protoscoleces, should be presented very careful, because of not to provoke suspicious of their verification^[87]. The oncosphere that undergo as metamorphosis toward metacystode could induce impaired response of IL-10 secreting DCs *in vitro*^[87]. These findings suggests that similar mechanisms might also further investigation by methods of primary cells could resolve the nature of echinococcal products responsible for these effects. But the effects at the beginning of infection with *E. granulosus* and that in chronic phases have not the same nature. They are late reduced, and leading to disappearance of FOXP3⁺-T-reg from microenvironment and decreased number of immature DCs in protoscoleces stage. Beside that the results are concentrated about *in vitro* interactions between parasite larvae and DCs in response to primary cells. No doubt that similar mechanisms operate in surrounding tissue in response to primary cells. This process might be important for early establishment of the parasite due to higher vulnerability of the host immune system. Later, after production of the laminar layer (LL) and activation of Treg cells, a slightly altered profile of excreted/secreted products could support long-term persistence and growth of the metacystode (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3283565/> - pntd.0001516-Mejri1)^[88]. Future investigations by using of genome sequence infor-

mation^[5,89], and other genetic manipulation of primary cells^[90], will give us opportunity for better understanding of the molecular mechanisms of parasite-host interactions.

CE AND AUTOIMMUNITY

Genetic predisposition in combination to others environmental factors have a decisive role in the induction of autoimmune reactions to *E. granulosus* and others parasitic infections. Genetically predisposed person with defective regulation of immune functions could be more receptive for autoimmune follow-up after parasite infections. A combination of autoimmunity environmental triggers and genetic factors can lead to immune imbalance and could influence the appearance of autoimmune diseases (Figure 3). CE and others parasitic disorders at their source will request the answer on question, why in some persons abnormal immune reactions arise more extensively than in others infected with the same parasite? To answer this question understanding of intrinsic mechanisms responsible for immune suppression need to be resolved. The well-known part of this mechanism is uncontrolled synthesis and elimination of self-reactive lymphocytes. Patients with CE showed increased number of T regulatory (Treg) cells, related cytokines such as IL-17 and IL-23, transcription factor FOXP3 and TGF β -1 level compared to control healthy subjects^[91]. The Th17/Treg balance controls inflammation and thus may play an important role in the pathogenesis of immune evasion^[91]. To estimate damage of this disbalance, Rosenblum *et al.*^[92] (2015) detected Th17/Treg functions at different levels of immune reaction by analyzing the cell frequencies, related cytokine secretions and key transcription factors in CE (Figure 3). Findings showed that a Th17/Treg functional disbalance in patients with chronic CE, suggesting a potential role for a Th17/Treg imbalance in the pathogenesis and immune evasion of *E. granulosus*. Regarding to genes associated with autoimmune diseases, the strongest associations with HLA alleles were detected^[93]. But, there are no data how different HLA alleles facilitate any autoimmune disease. Bearing in mind that many HLA alleles are capable to present self-antigens in healthy and in infected subjects, it is not clear how different HLA alleles influences autoimmune diseases. It is unlikely that a disease-associated allele is especially efficient at displaying the autoantigens targeted by self-reactive T cells due to most HLA alleles are capable of presenting self-antigens also in healthy subjects. Yet, most healthy individuals have autoreactive T cells that escape thymic deletion^[94,95].

Genetic susceptibility to host autoimmunity

Knowledge of genes that are involved in induction of autoimmune diseases are discouraging, and is in lower level than those for HLA alleles. Completely different, genetic polymorphism of cytokine and cytokine receptors are well examined. Findings indicate that cytokines have been linked to many different autoimmune diseases, and IL-23 and IL-23R augmenting inflammatory capability of Th17 cells^[94,95]. In that way, IL-23R have been discovered in ankylosing

spondylitis, Behcet's disease, Crohn's disease, psoriasis, and ulcerative colitis^[96]. Moreover, in all of these diseases IL-17 positive inflammatory cells have also been associated with tissue damage in all mentioned disorders. By using of monoclonal antibodies specific for either p40 (a subunit of IL-23) or IL-17A their efficacy were confirmed in almost all of these disorders^[43,97]. Thus, genetic polymorphisms in IL-23R have in some cases been correlated with responses to targeted anti-cytokine therapies. Nevertheless the development of many human autoimmune diseases is result of reaction of multiple genes involved. There is opinion that gene polymorphism is responsible for the most human autoimmune diseases. Only a few examples existing in which genetic alterations in a single gene result in severe autoimmune syndroms. The two best examined monogenetic autoimmune syndroms resulting from the mutations in *AIRE* and *FOXP3* genes are autoimmune polyendocrine syndrome (APS) and immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome^[98,99]. These mutations leading to dysfunction in central (APS) and peripheral (IPEX) tolerance. Another example of autoimmune lymphoproliferative disfunction of Fas gene, Fas ligand or of in caspases downstream of Fas signaling, resulting in a defective Fas-mediated apoptosis and chronic lymphoproliferative causing lymphadenopathy, splenomegaly, and autoimmune cytopenias^[100]. Discovering of the single genes responsible for development of aforementioned autoimmune disorders has greatly contribution in our understanding of cellular and subcellular mechanisms responsible for the development and follow-up of many by parasite induced autoimmune diseases.

Environmental factors in host autoimmunity

Environmental triggers are factors originating outside of the body, such as parasites, bacteria, viruses, toxins and medications. No doubt that infections could be important triggering factor for autoimmune dysfunctions^[101,102]. Many theories have been created to explain this connection and excessive innate/pattern recognition receptor activation in autoimmunity. Epitope spreading and antigenic complementarity are few between many theories proposed. There is evidence that the presence of *Epstein bar virus* in postmortem brain tissue has been linked with appearance of Multiple sclerosis (MS), but not with other autoimmune inflammatory diseases^[103]. Furthermore, periodontal infections and rheumatoid arthritis are also linked with autoimmunity induced by infection^[104]. In contrary, ideas existing that infection could protect from some autoimmune disorders. Thus germ-free mice exposed to *Bacteroides fragilis* could be protected from development of experimental autoimmune encephalomyelitis (EAE), by induction of Treg cells^[105]. In that way, a higher incidence of MS and type 1 diabetes in developed countries is supposed to correlate with decreased number of infections^[106].

Defective regulation as the cause of autoimmunity

The peripheral tolerance to tissue antigens could be induced by the low-level of natural cell death through

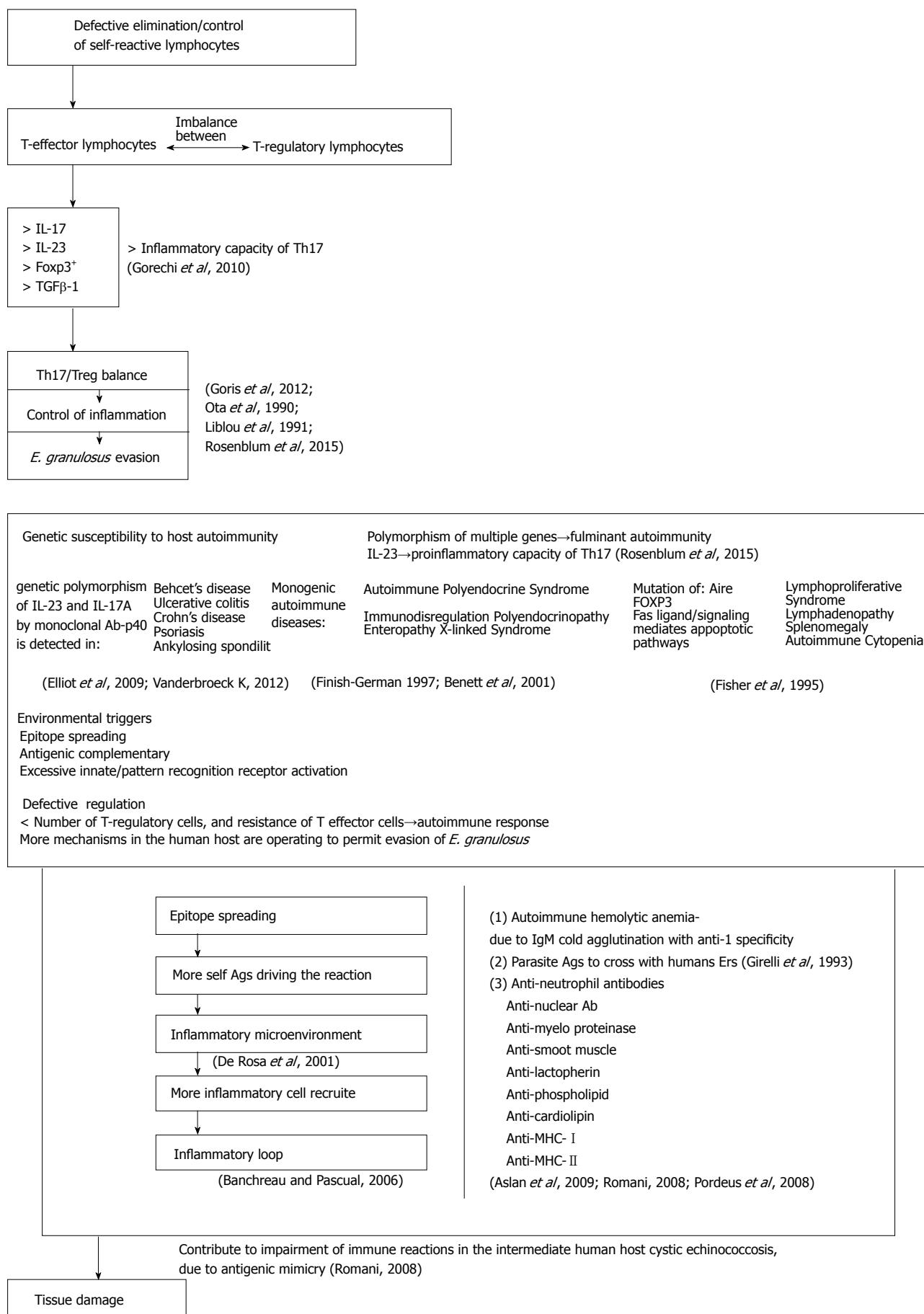


Figure 3 *Echinococcus granulosus* Induced autoimmunity. Ags: Antigens.

the tolerance of dendritic cell populations^[107]. This tolerance can influence low level of natural cell death in the tissue antigens, respectively^[107]. If tolerance is the main abnormality in autoimmune processes, which kind of tolerance is processed in induction of autoimmune diseases? In SLE it is maturation of naïve B cells that can produce autoantibodies even before encountering with antigens. Findings that defects in early B cell tolerance checkpoints possible contribute development of an autoimmune disease^[108]. Beside others, deletion cross influences B cell maturation of immature B cells in the bone marrow, receptor editing, and the control of mature B cells in peripheral tissues^[108].

Regarding T cell-dependent autoimmunity and inflammatory autoimmune diseases, imbalance between effector and regulatory T cells play a fundamental role in initiation of human autoimmune diseases^[109].

Decreased number of functional T regulatory or resistance of effector T cells play decisive role in the initiation of autoimmune diseases in human. Obtained results from patients with autoimmune disorders are often variable and inconsistent, due to the limited assessability of tissue for examination. Even when an optimal number of cells for analysis is supplied, *in vitro* assays that often cannot be recapitulated, is not reliable for examination of functional capacity *in vivo*. The disease in autoimmunity might be explained by self-perpetuating ability of autoimmune reactions. The self-antigen that drive autoimmune reaction remain functional and cannot be eliminated from the organism due to the emergency of a new antigenic epitopes in damaged tissue and alterations of self-proteins. This process is known as antigen epitope spreading phenomenon, and a vicious cycle is set-up.

Longitudinal studies of effector and Treg cells that are specific for target self-antigens in human disease remain a considerable technical challenge. Newly created antigenic epitopes activate more different lymphocytes in autoimmune reaction, leading to more tissue damage, and more novel epitopes to autoreactive lymphocytes. In that way, potentiated autoimmune reaction creates a new convenient environment for activation of multiple immune cells, cytokines and other mediators that amplify autoimmune reaction with catastrophic results to patient. In that way IFN- γ production may induce SLE. Then inflammation in SLE showed is involved in the propagation of the disease^[110]. The prolonged survival of *E. granulosus* metacestodes within the human host indicates that some mechanisms are operating to permit evasion of the host immune response. Several authors tried to describe autoimmune phenomena in patients with CE. Autoimmune hemolytic anemia due to IgM cold agglutinin with anti-I specificity was found to be induced in patients with CE. Moreover, the cleavage fragment of C3 has been detected on the erythrocyte membrane of a number of CE patients, suggesting that parasitic antigens may evoke antibodies that cross with human erythrocytes^[111]. Furthermore, anti-neutrophil cytoplasmic, anti-myeloperoxidase and anti-lactoferrin antibodies have also been revealed in the sera of CE patients^[112].

However, no significant correlations have been observed between CE and anti-nuclear antibodies, tissue specific autoantibodies and rheumatoid factors. In contrast, Aslan and coworkers have measured significant levels of antinuclear antibodies, anti-mitochondrial and anti-smooth muscle antibodies in patients with CE in comparison to age- and sex-matched healthy individuals^[113]. Anti-phospholipid antibodies, anti-cardiolipin antibodies and anti-dsDNA have also been shown to be associated with several infectious diseases and some autoimmune diseases such as systemic lupus erythematosus and anti-phospholipid syndrome. Such elevated levels of these antibodies could be explained by the antigenic mimicry between the parasite antigens and host proteins^[114]. Since cardiolipin and phospholipids are abundant in most cells of multicellular organisms, the former is an important component of the inner mitochondrial membrane, where it constitutes approximately 20% of the total lipid composition, while phospholipids are a class of lipids and a major component of all cell membranes as they can form a lipid bilayer^[115,116]. Moreover, autoantibodies class I and class II MHC gene products have also been demonstrated in CE patients, which may contribute to impairment of the host immune responses. Chronic and multiple infections with viruses, such as Epstein-Barr virus, cytomegalovirus and bacteria, such as *H. pylori*, may also be involved in the development of an autoimmune disease in susceptible individuals^[117].

Finally, the parasites survive well in the human host and the host attempting to destroy them^[118]. From a promotional perspective, knowledge of immune events to response on infection with a helminth parasite could be used to reduce the intensity of undesirable inflammatory reactions. But, poorly characterized cestode extracts cannot help the regulation of human immunocyte function. Yet the impact of these for treatment of autoimmune or allergic diseases is poorly understood. No doubt that helminth parasites are masters for immune evasion and regulation. A likely prerequisite for long-term survival is outwit of their host's attempt to eradicate them^[119].

CONCLUSION

E. granulosus is very complex multicellular parasite. As many pathogens is highly immunogenic for human host. Thus, the host immunity play a most important role in host-parasite relationship in human echinococcosis. The secretory and excretory products from parasite influences immune and immune competent cells in human host and stimulate humoral and proinflammatory cell-mediated immune responses, releasing of significant antibody production, and activate T cells and other antigen-presenting cells in human host. Thus, the understanding of the immune mechanisms is of fundamental importance for revealing of a basic protective processes in human with hydatidosis. No doubt that protective antibodies are also extremely important for development of a new more effective vaccines against *E. granulosus* and other parasites. Knowledge of immune events as a response to

infection with a helminth parasite could be used to reduce the intensity of undesired immune and autoimmune reactions such as a variety of auto-inflammatory diseases and allergy. Relevant findings is accumulating showing that inflammatory reactions that promote a variety of auto-inflammatory disease are dampened as a consequence of infection with helminth parasites *via* either the mobilization of anti-worm spectrum of immune reactions or direct effects of bioactive immunomodulatory molecules and chemical compounds released from the parasite. Also the cestode extracts are poorly characterized and their impact on autoimmune and allergic diseases are not fully examined due to the mechanisms of reaction are not understood. Yet issues related to this topics regarding purification of immunomodulatory molecules, their site effects and action to parasites remains as challenges that need to be addressed.

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REFERENCES

- Caremani M, Benci A, Maestrini R, Rossi G, Menchetti D. Abdominal cystic hydatid disease (CHD): classification of sonographic appearance and response to treatment. *J Clin Ultrasound* 1996; **24**: 491-500 [PMID: 8906480 DOI: 10.1002/(SICI)1097-0096(199611/12)24:93.0.CO;2-I]
- Rinaldi F, Brunetti E, Neumayr A, Maestri M, Goblirsch S, Tamarozzi F. Cystic echinococcosis of the liver: A primer for hepatologists. *World J Hepatol* 2014; **6**: 293-305 [PMID: 24868323 DOI: 10.4254/wjh.v6.i5.293]
- Pakala T, Molina M, Wu GY. Hepatic Echinococcal Cysts: A Review. *J Clin Transl Hepatol* 2016; **4**: 39-46 [PMID: 27047771 DOI: 10.14218/JCTH.2015.00036]
- Brehm K. The role of evolutionarily conserved signalling systems in Echinococcus multilocularis development and host-parasite interaction. *Med Microbiol Immunol* 2010; **199**: 247-259 [PMID: 20376483 DOI: 10.1007/s00430-010-0154-1]
- Brehm K. Echinococcus multilocularis as an experimental model in stem cell research and molecular host-parasite interaction. *Parasitology* 2010; **137**: 537-555 [PMID: 19961652 DOI: 10.1017/S0031182009991727]
- Eckert J, Deplazes P. Biological, epidemiological, and clinical aspects of echinococcosis, a zoonosis of increasing concern. *Clin Microbiol Rev* 2004; **17**: 107-135 [PMID: 14726458]
- Pedrosa I, Saiz A, Arrazola J, Ferreirós J, Pedrosa CS. Hydatid disease: radiologic and pathologic features and complications. *Radiographics* 2000; **20**: 795-817 [PMID: 10835129 DOI: 10.1148/radiographics.20.3.g00ma06795]
- Menezes da Silva A. Human Echinococcosis: A Neglected Disease. In: Senturk H, editor. Gastroenterology Research and Practice. Hindawi Publishing Corporation: Cairo. Gastroenterology Research and Practice 2010; 2010: 1-9
- Vagianos CE, Karavias DD, Kakkos SK, Vagenas CA, Androulakis JA. Conservative surgery in the treatment of hepatic hydatidosis. *Eur J Surg* 1995; **161**: 415-420 [PMID: 7548377]
- Karavias DD, Vagianos CE, Kakkos SK, Panagopoulos CM, Androulakis JA. Peritoneal echinococcosis. *World J Surg* 1996; **20**: 337-340 [PMID: 8661841 DOI: 10.1007/s002689900054]
- Siracusano A, Delunardo F, Teggi A, Ortona E. Cystic echinococcosis: aspects of immune response, immunopathogenesis and immune evasion from the human host. *Endocr Metab Immune Disord Drug Targets* 2012; **12**: 16-23 [PMID: 22214328 DOI: 10.2174/187153012799279117]
- Zhang W, Ross AG, McManus DP. Mechanisms of immunity in hydatid disease: implications for vaccine development. *J Immunol* 2008; **181**: 6679-6685 [PMID: 18981082]
- Siracusano A, Riganò R, Ortona E, Profumo E, Margutti P, Buttari B, Delunardo F, Teggi A. Immunomodulatory mechanisms during Echinococcus granulosus infection. *Exp Parasitol* 2008; **119**: 483-489 [PMID: 18329023 DOI: 10.1016/j.exppara.2008.01.016]
- Riganò R, Profumo E, Buttari B, Teggi A, Siracusano A. Cytokine gene expression in peripheral blood mononuclear cells (PBMC) from patients with pharmacologically treated cystic echinococcosis. *Clin Exp Immunol* 1999; **118**: 95-101 [PMID: 10540165 DOI: 10.1046/j.1365-2249.1999.01021.x]
- Amri M, Mezioug D, Touil-Boukoffa C. Involvement of IL-10 and IL-4 in evasion strategies of Echinococcus granulosus to host immune response. *Eur Cytokine Netw* 2009; **20**: 63-68 [PMID: 19541591 DOI: 10.1684/ecn.2009.0154]
- Riganò R, Profumo E, Teggi A, Siracusano A. Production of IL-5 and IL-6 by peripheral blood mononuclear cells (PBMC) from patients with Echinococcus granulosus infection. *Clin Exp Immunol* 1996; **105**: 456-459 [PMID: 8809134 DOI: 10.1046/j.1365-2249.1996.d01-796.x]
- al-Tuwaijri AS, al-Dohayan AD. The pattern of respiratory burst of leucocytes in patients with Echinococcus granulosus. *Microbios* 1995; **83**: 167-174 [PMID: 8559081]
- Virginio VG, Taroco L, Ramos AL, Ferreira AM, Zaha A, Ferreira HB, Hernández A. Effects of protoscoleces and AgB from Echinococcus granulosus on human neutrophils: possible implications on the parasite's immune evasion mechanisms. *Parasitol Res* 2007; **100**: 935-942 [PMID: 17111175 DOI: 10.1007/s00436-006-0366-x]
- Huguier M, Leynadier F, Houry S, Lacaine F, Dry J. Human basophil degranulation test in liver hydatidosis. *Dig Dis Sci* 1987; **32**: 1354-1357 [PMID: 3691275]
- Aceti A, Celestino D, Caferro M, Teggi A, Pennica A, Adriani E, Grilli A, Paparo S, Leri O, De Rosa F. Basophil releasability in human hydatidosis. *Int Arch Allergy Appl Immunol* 1990; **91**: 111-112 [PMID: 1690179]
- Aceti A, Celestino D, Teggi A, Caferro M. Spontaneous in vitro generation of histamine releasing factor from mononuclear cells of patients with hydatidosis. *Int Arch Allergy Immunol* 1992; **98**: 247-251 [PMID: 1382747]
- Riganò R, Profumo E, Di Felice G, Ortona E, Teggi A, Siracusano A. In vitro production of cytokines by peripheral blood mononuclear cells from hydatid patients. *Clin Exp Immunol* 1995; **99**: 433-439 [PMID: 7882566 DOI: 10.1111/j.1365-2249.1995.tb05569.x]
- Hernández-Pomí A, Borrás-Salvador R, Mir-Gisbert A. Analysis of cytokine and specific antibody profiles in hydatid patients with primary infection and relapse of disease. *Parasite Immunol* 1997; **19**: 553-561 [PMID: 9458467 DOI: 10.1046/j.1365-3024.1997.d01-173.x]
- Ferreira AM, Würzner R, Hobart MJ, Lachmann PJ. Study of the in vitro activation of the complement alternative pathway by Echinococcus granulosus hydatid cyst fluid. *Parasite Immunol* 1995; **17**: 245-251 [PMID: 7675511 DOI: 10.1111/pim.12282]
- Díaz A, Ferreira AM, Nieto A. Echinococcus granulosus: interactions with host complement in secondary infection in mice. *Exp Parasitol* 1995; **80**: 473-482 [PMID: 7729482 DOI: 10.1006/expr.1995.1059]
- Baveja UK, Basak S, Thusoo TK. A study of immune profile in human hydatid diseases. *J Commun Dis* 1995; **27**: 61-69 [PMID: 7499774]
- Irgoin F, Würzner R, Sim RB, Ferreira AM. Comparison of complement activation in vitro by different Echinococcus granulosus extracts. *Parasite Immunol* 1996; **18**: 371-375 [PMID: 9229390 DOI: 10.1046/j.1365-3024.1996.d01-112.x]
- Zhang W, You H, Li J, Zhang Z, Turson G, Aili H, Wang J, McManus DP. Immunoglobulin profiles in a murine intermediate host model of resistance for Echinococcus granulosus infection. *Parasite Immunol* 2003; **25**: 161-168 [PMID: 12911524]
- Zhang W, Li J, Jones MK, Zhang Z, Zhao L, Blair D, McManus DP.

- The *Echinococcus granulosus* antigen B gene family comprises at least 10 unique genes in five subclasses which are differentially expressed. *PLoS Negl Trop Dis* 2010; **4**: e784 [PMID: 20706625 DOI: 10.1371/journal.pntd.0000784]
- 30 **Chemale G**, Haag KL, Ferreira HB, Zaha A. *Echinococcus granulosus* antigen B is encoded by a gene family. *Mol Biochem Parasitol* 2001; **116**: 233-237 [PMID: 11522357]
 - 31 **Chemale G**, Ferreira HB, Barrett J, Brophy PM, Zaha A. *Echinococcus granulosus* antigen B hydrophobic ligand binding properties. *Biochim Biophys Acta* 2005; **1747**: 189-194 [PMID: 15698953 DOI: 10.1016/j.bbapap.2004.11.004]
 - 32 **Shepherd JC**, Aitken A, McManus DP. A protein secreted in vivo by *Echinococcus granulosus* inhibits elastase activity and neutrophil chemotaxis. *Mol Biochem Parasitol* 1991; **44**: 81-90 [PMID: 2011156]
 - 33 **Riganò R**, Profumo E, Bruschi F, Carulli G, Azzarà A, Ioppolo S, Buttari B, Ortona E, Margutti P, Teggi A, Siracusano A. Modulation of human immune response by *Echinococcus granulosus* antigen B and its possible role in evading host defenses. *Infect Immun* 2001; **69**: 288-296 [PMID: 11119517 DOI: 10.1128/IAI.69.1.288-296.2001]
 - 34 **Everts B**, Smits HH, Hokke CH, Yazdanbakhsh M. Helminths and dendritic cells: sensing and regulating via pattern recognition receptors, Th2 and Treg responses. *Eur J Immunol* 2010; **40**: 1525-1537 [PMID: 20405478 DOI: 10.1002/eji.200940109]
 - 35 **Nono JK**, Pletinckx K, Lutz MB, Brehm K. Excretory/secretory-products of *Echinococcus multilocularis* larvae induce apoptosis and tolerogenic properties in dendritic cells in vitro. *PLoS Negl Trop Dis* 2012; **6**: e1516 [PMID: 22363826 DOI: 10.1371/journal.pntd.0001516]
 - 36 **Paredes R**, Godoy P, Rodríguez B, García MP, Cabezón C, Cabrera G, Jiménez V, Hellman U, Sáenz L, Ferreira A, Galanti N. Bovine (*Bos taurus*) humoral immune response against *Echinococcus granulosus* and hydatid cyst infertility. *J Cell Biochem* 2011; **112**: 189-199 [PMID: 21117064 DOI: 10.1002/jcb.22916]
 - 37 **Maizels RM**, Balic A, Gomez-Escobar N, Nair M, Taylor MD, Allen JE. Helminth parasites--masters of regulation. *Immunol Rev* 2004; **201**: 89-116 [PMID: 15361235 DOI: 10.1111/j.0105-2896.2004.00191.x]
 - 38 **Vignali DA**, Collison LW, Workman CJ. How regulatory T cells work. *Nat Rev Immunol* 2008; **8**: 523-532 [PMID: 18566595 DOI: 10.1038/nri2343]
 - 39 **Pawlowski Z**. Echinococcosis in humans: clinical aspects, diagnosis and treatment, in WHO/OIE manual on echinococcosis in humans and animals: public health problem of global concern. Paris, France: WHO/OIE, 2001: 20-60 [DOI: 10.1017/S0022149X01000464]
 - 40 **Garraud O**, Perraut R, Riveau G, Nutman TB. Class and subclass selection in parasite-specific antibody responses. *Trends Parasitol* 2003; **19**: 300-304 [PMID: 12855380]
 - 41 **Yazdanbakhsh M**, Krensmeyer PG, van Ree R. Allergy, parasites, and the hygiene hypothesis. *Science* 2002; **296**: 490-494 [PMID: 11964470 DOI: 10.1126/science.296.5567.490]
 - 42 **Ortona E**, Vaccari S, Margutti P, Delunardo F, Riganò R, Profumo E, Buttari B, Rasool O, Teggi A, Siracusano A. Immunological characterization of *Echinococcus granulosus* cyclophilin, an allergen reactive with IgE and IgG4 from patients with cystic echinococcosis. *Clin Exp Immunol* 2002; **128**: 124-130 [PMID: 11982600]
 - 43 **Elliott M**, Benson J, Blank M, Brodmerkel C, Baker D, Sharples KR, Szapary P. Ustekinumab: lessons learned from targeting interleukin-12/23p40 in immune-mediated diseases. *Ann N Y Acad Sci* 2009; **1182**: 97-110 [PMID: 20074279 DOI: 10.1111/j.1749-6632.2009.05070.x]
 - 44 **Margutti P**, Ortona E, Vaccari S, Barca S, Riganò R, Teggi A, Muhschlegel F, Frosch M, Siracusano A. Cloning and expression of a cDNA encoding an elongation factor 1 beta/delta protein from *Echinococcus granulosus* with immunogenic activity. *Parasite Immunol* 1999; **21**: 485-492 [PMID: 10476057 DOI: 10.1046/j.1365-3024.1999.00246]
 - 45 **Ortona E**, Margutti P, Vaccari S, Riganò R, Profumo E, Buttari B, Chersi A, Teggi A, Siracusano A. Elongation factor 1 beta/delta of *Echinococcus granulosus* and allergic manifestations in human cystic echinococcosis. *Clin Exp Immunol* 2001; **125**: 110-116 [PMID: 11472433 DOI: 10.1046/j.1365-2249.2001.01569.x]
 - 46 **Ortona E**, Margutti P, Delunardo F, Nobili V, Profumo E, Riganò R, Buttari B, Carulli G, Azzarà A, Teggi A, Bruschi F, Siracusano A. Screening of an *Echinococcus granulosus* cDNA library with IgG4 from patients with cystic echinococcosis identifies a new tegumental protein involved in the immune escape. *Clin Exp Immunol* 2005; **142**: 528-538 [PMID: 16297166 DOI: 10.1111/j.1365-2249.2005.02939.x]
 - 47 **Ortona E**, Margutti P, Delunardo F, Vaccari S, Riganò R, Profumo E, Buttari B, Teggi A, Siracusano A. Molecular and immunological characterization of the C-terminal region of a new *Echinococcus granulosus* Heat Shock Protein 70. *Parasite Immunol* 2003; **25**: 119-126 [PMID: 12911519 DOI: 10.1046/j.1365-3024.2003.00617.x]
 - 48 **Kakkos SK**, Mouzaki A, Vagianos CE. Modification of the immune system caused by the cestode *Echinococcus granulosus*: A review. *Annals of Gastroenterology* 2001; **14**: 91-98
 - 49 **Chemale G**, van Rossum AJ, Jefferies JR, Barrett J, Brophy PM, Ferreira HB, Zaha A. Proteomic analysis of the larval stage of the parasite *Echinococcus granulosus*: causative agent of cystic hydatid disease. *Proteomics* 2003; **3**: 1633-1636 [PMID: 12923787 DOI: 10.1002/pmic.200300487]
 - 50 **Monteiro KM**, de Carvalho MO, Zaha A, Ferreira HB. Proteomic analysis of the *Echinococcus granulosus* metacestode during infection of its intermediate host. *Proteomics* 2010; **10**: 1985-1999 [PMID: 20217864 DOI: 10.1002/pmic.200900506]
 - 51 **Jankovic D**, Liu Z, Gause WC. Th1- and Th2-cell commitment during infectious disease: asymmetry in divergent pathways. *Trends Immunol* 2001; **22**: 450-457 [PMID: 11473835 DOI: 10.1016/S1471-4906(01)01975-5]
 - 52 **Baz A**, Ettlin GM, Dematteis S. Complexity and function of cytokine responses in experimental infection by *Echinococcus granulosus*. *Immunobiology* 2006; **211**: 3-9 [PMID: 16446166 DOI: 10.1016/j.imbio.2005.09.001]
 - 53 **Vuitton DA**, Gottstein B. *Echinococcus multilocularis* and its intermediate host: a model of parasite-host interplay. *J Biomed Biotechnol* 2010; **2010**: 923193 [PMID: 20339517 DOI: 10.1155/2010/923193]
 - 54 **Riganò R**, Buttari B, De Falco E, Profumo E, Ortona E, Margutti P, Scottà C, Teggi A, Siracusano A. *Echinococcus granulosus*-specific T-cell lines derived from patients at various clinical stages of cystic echinococcosis. *Parasite Immunol* 2004; **26**: 45-52 [PMID: 15198645 DOI: 10.1111/j.0141-9838.2004.00682.x]
 - 55 **Riganò R**, Buttari B, Profumo E, Ortona E, Delunardo F, Margutti P, Mattei V, Teggi A, Sorice M, Siracusano A. *Echinococcus granulosus* antigen B impairs human dendritic cell differentiation and polarizes immature dendritic cell maturation towards a Th2 cell response. *Infect Immun* 2007; **75**: 1667-1678 [PMID: 17210662 DOI: 10.1128/IAI.01156-06]
 - 56 **Riganò R**, Profumo E, Ioppolo S, Notargiacomo S, Teggi A, Siracusano A. Cytokine patterns in seropositive and seronegative patients with *Echinococcus granulosus* infection. *Immunol Lett* 1998; **64**: 5-8 [PMID: 9865595 DOI: 10.1016/S0165-2478(98)00072-8]
 - 57 **Sher A**, Pearce E, Kaye P. Shaping the immune response to parasites: role of dendritic cells. *Curr Opin Immunol* 2003; **15**: 421-429 [PMID: 12900274 DOI: 10.1016/S0952-7915]
 - 58 **Jankovic D**, Steinfelder S, Kullberg MC, Sher A. Mechanisms underlying helminth-induced Th2 polarization: default, negative or positive pathways? *Chem Immunol Allergy* 2006; **90**: 65-81 [PMID: 16210903 DOI: 10.1159/000088881]
 - 59 **Kanan JH**, Chain BM. Modulation of dendritic cell differentiation and cytokine secretion by the hydatid cyst fluid of *Echinococcus granulosus*. *Immunology* 2006; **118**: 271-278 [PMID: 16771863 DOI: 10.1111/j.1365-2567.2006.02375.x]
 - 60 **MacDonald AS**, Maizels RM. Alarming dendritic cells for Th2 induction. *J Exp Med* 2008; **205**: 13-17 [PMID: 18195077 DOI: 10.1084/jem.20072665]
 - 61 **Banchereau J**, Briere F, Caux C, Davoust J, Lebecque S, Liu YJ, Pulendran B, Palucka K. Immunobiology of dendritic cells. *Annu Rev Immunol* 2000; **18**: 767-811 [PMID: 10837075 DOI: 10.1146/annurev.immunol.18.1.767]
 - 62 **Grainger JR**, Hall JA, Bouladoux N, Oldenhove G, Belkaid Y. Microbe-dendritic cell dialog controls regulatory T-cell fate. *Immunol Rev* 2010; **234**: 305-316 [PMID: 20193027 DOI: 10.1111/

- j.0105-2896.2009.00880.x]
- 63 **Mejri N**, Müller N, Hemphill A, Gottstein B. Intraperitoneal *Echinococcus multilocularis* infection in mice modulates peritoneal CD4⁺ and CD8⁺ regulatory T cell development. *Parasitol Int* 2011; **60**: 45-53 [PMID: 20965274 DOI: 10.1016/j.parint.2010.10.002]
 - 64 **Tappe D**, Weise D, Ziegler U, Müller A, Müllges W, Stich A. Brain and lung metastasis of alveolar echinococcosis in a refugee from a hyperendemic area. *J Med Microbiol* 2008; **57**: 1420-1423 [PMID: 18927422 DOI: 10.1099/jmm.0.2008/002816-0]
 - 65 **Maizels RM**, Pearce EJ, Artis D, Yazdanbakhsh M, Wynn TA. Regulation of pathogenesis and immunity in helminth infections. *J Exp Med* 2009; **206**: 2059-2066 [PMID: 19770272 DOI: 10.1084/jem.20091903]
 - 66 **Reyes JL**, Terrazas CA, Vera-Arias L, Terrazas LI. Differential response of antigen presenting cells from susceptible and resistant strains of mice to *Taenia crassiceps* infection. *Infect Genet Evol* 2009; **9**: 1115-1127 [PMID: 19465163 DOI: 10.1016/j.meegid.2009.05.011]
 - 67 **Terrazas CA**, Gómez-García L, Terrazas LI. Impaired pro-inflammatory cytokine production and increased Th2-biasing ability of dendritic cells exposed to *Taenia* excreted/secreted antigens: A critical role for carbohydrates but not for STAT6 signaling. *Int J Parasitol* 2010; **40**: 1051-1062 [PMID: 20361966 DOI: 10.1016/j.ijpara.2010.02.016]
 - 68 **Siracusano A**, Margutti P, Delunardo F, Profumo E, Riganò R, Buttari B, Teggi A, Ortona E. Molecular cross-talk in host-parasite relationships: the intriguing immunomodulatory role of *Echinococcus* antigen B in cystic echinococcosis. *Int J Parasitol* 2008; **38**: 1371-1376 [PMID: 18692060 DOI: 10.1016/j.ijpara.2008.06.003]
 - 69 **Bernthaler P**, Epping K, Schmitz G, Deplazes P, Brehm K. Molecular characterization of EmABP, an apolipoprotein A-I binding protein secreted by the *Echinococcus multilocularis* metacestode. *Infect Immun* 2009; **77**: 5564-5571 [PMID: 19805524 DOI: 10.1128/IAI.00653-09]
 - 70 **Jenne L**, Arrighi JF, Sauter B, Kern P. Dendritic cells pulsed with unfractionated helminthic proteins to generate antiparasitic cytotoxic T lymphocyte. *Parasite Immunol* 2001; **23**: 195-201 [PMID: 11298296 DOI: 10.1046/j.1365-3024.2001.00374.x]
 - 71 **Hülsmeier AJ**, Gehrig PM, Geyer R, Sack R, Gottstein B, Deplazes P, Köhler P. A major *Echinococcus multilocularis* antigen is a mucin-type glycoprotein. *J Biol Chem* 2002; **277**: 5742-5748 [PMID: 11729180 DOI: 10.1074/jbc.M107161200]
 - 72 **Margos MC**, Grandgirard D, Leib S, Gottstein B. In vitro induction of lymph node cell proliferation by mouse bone marrow dendritic cells following stimulation with different *Echinococcus multilocularis* antigens. *J Helminthol* 2011; **85**: 128-137 [PMID: 21226990 DOI: 10.1017/S0022149X10000878]
 - 73 **Kushwah R**, Hu J. Dendritic cell apoptosis: regulation of tolerance versus immunity. *J Immunol* 2010; **185**: 795-802 [PMID: 20601611 DOI: 10.4049/jimmunol.1000325]
 - 74 **Semnani RT**, Liu AY, Sabzevari H, Kubofcik J, Zhou J, Gilden JK, Nutman TB. *Brugia malayi* microfilariiae induce cell death in human dendritic cells, inhibit their ability to make IL-12 and IL-10, and reduce their capacity to activate CD4⁺ T cells. *J Immunol* 2003; **171**: 1950-1960 [PMID: 12902498 DOI: 10.4049/jimmunol.171.4.1950]
 - 75 **Freitas TC**, Pearce EJ. Growth factors and chemotactic factors from parasitic helminths: molecular evidence for roles in host-parasite interactions versus parasite development. *Int J Parasitol* 2010; **40**: 761-773 [PMID: 20359480 DOI: 10.1016/j.ijpara.2010.02.013]
 - 76 **McSorley HJ**, Grainger JR, Hargus Y, Murray J, Nisbet AJ, Knox DP, Maizels RM. daf-7-related TGF- β homologues from *Trichostrongylid* nematodes show contrasting life-cycle expression patterns. *Parasitology* 2010; **137**: 159-171 [PMID: 19712539 DOI: 10.1017/S003118200990321]
 - 77 **Olson PD**, Zarowiecki M, Kiss F, Brehm K. Cestode genomics - progress and prospects for advancing basic and applied aspects of flatworm biology. *Parasite Immunol* 2012; **34**: 130-150 [PMID: 21793855 DOI: 10.1111/j.1365-3024.2011.01319.x]
 - 78 **Pletinckx K**, Stijlemans B, Pavlovic V, Laube R, Brandl C, Kneitz S, Beschin A, De Baetselier P, Lutz MB. Similar inflammatory DC maturation signatures induced by TNF or *Trypanosoma brucei* antigens instruct default Th2-cell responses. *Eur J Immunol* 2011; **41**: 3479-3494 [PMID: 21928284 DOI: 10.1002/eji.201141631]
 - 79 **Matsumoto J**, Kouguchi H, Oku Y, Yagi K. Primary alveolar echinococcosis: course of larval development and antibody responses in intermediate host rodents with different genetic backgrounds after oral infection with eggs of *Echinococcus multilocularis*. *Parasitol Int* 2010; **59**: 435-444 [PMID: 20601109 DOI: 10.1016/j.parint.2010.06.003]
 - 80 **McKay DM**, Webb RA. Cestode infection: immunological considerations from host and tapeworm perspectives. In: Maule AG, Marks NJ, editors. *Parasitic flatworms: molecular biology, biochemistry, immunology and physiology*. Wallingford, United Kingdom: CABI publishing, 2005: 193-209
 - 81 **Cox DA**, Marshall-Clarke S, Dixon JB. Activation of normal murine B cells by *Echinococcus granulosus*. *Immunology* 1989; **67**: 16-20 [PMID: 2661414]
 - 82 **Kizaki T**, Ishige M, Bingyan W, Day NK, Good RA, Onoé K. Generation of CD8⁺ suppressor T cells by protoscoleces of *Echinococcus multilocularis* in vitro. *Immunology* 1993; **79**: 412-417 [PMID: 8104883]
 - 83 **Kizaki T**, Ishige M, Bingyan W, Kumagai M, Day NK, Good RA, Onoé K. Interleukin-1-dependent mitogenic responses induced by protoscoleces of *Echinococcus multilocularis* in murine lymphocytes. *J Leukoc Biol* 1993; **53**: 233-239 [PMID: 8454946]
 - 84 **Kizaki T**, Ishige M, Kobayashi S, Bingyan W, Kumagai M, Day NK, Good RA, Onoé K. Suppression of T-cell proliferation by CD8⁺ T cells induced in the presence of protoscolices of *Echinococcus multilocularis* in vitro. *Infect Immun* 1993; **61**: 525-533 [PMID: 8423083]
 - 85 **Kizaki T**, Kobayashi S, Ogasawara K, Day NK, Good RA, Onoé K. Immune suppression induced by protoscoleces of *Echinococcus multilocularis* in mice. Evidence for the presence of CD8⁺dull suppressor cells in spleens of mice intraperitoneally infected with *E. multilocularis*. *J Immunol* 1991; **147**: 1659-1666 [PMID: 1831831]
 - 86 **Macintyre AR**, Dixon JB. *Echinococcus granulosus*: regulation of leukocyte growth by living protoscoleces from horses, sheep, and cattle. *Exp Parasitol* 2001; **99**: 198-205 [PMID: 11888246 DOI: 10.1006/expr.2001.4662]
 - 87 **Gabrion C**, Walbaum S, al Nahhas S, Mesnil M, Petavy AF. *Echinococcus multilocularis* protoscoleces and hepatic cell activity in vitro. *Int J Parasitol* 1995; **25**: 127-130 [PMID: 7797364 DOI: 10.1007/BF00932375]
 - 88 **Dvoroznáková E**, Porubcová J, Sevcíková Z. Immune response of mice with alveolar echinococcosis to therapy with transfer factor, alone and in combination with albendazole. *Parasitol Res* 2009; **105**: 1067-1076 [PMID: 19548004 DOI: 10.1007/s00436-009-1520-z]
 - 89 **Jenne L**, Arrighi JF, Jonuleit IT, Saurat JH, Hauser C. Dendritic cells containing apoptotic melanoma cells prime human CD8⁺ T cells for efficient tumor cell lysis. *Cancer Research* 2000; **60**: 4446-4452
 - 90 **Spiliotis M**, Mizukami C, Oku Y, Kiss F, Brehm K, Gottstein B. *Echinococcus multilocularis* primary cells: improved isolation, small-scale cultivation and RNA interference. *Mol Biochem Parasitol* 2010; **174**: 83-87 [PMID: 20637246 DOI: 10.1016/j.molbiopara.2010.07.001]
 - 91 **Ghoreschi K**, Laurence A, Yang XP, Tato CM, McGeachy MJ, Konkel JE, Ramos HL, Wei L, Davidson TS, Bouladoux N, Grainger JR, Chen Q, Kanno Y, Watford WT, Sun HW, Eberl G, Shevach EM, Belkaid Y, Cua DJ, Chen W, O'Shea JJ. Generation of pathogenic T(H)17 cells in the absence of TGF- β signalling. *Nature* 2010; **467**: 967-971 [PMID: 20962846 DOI: 10.1038/nature09447]
 - 92 **Rosenblum MD**, Remedios KA, Abbas AK. Mechanisms of human autoimmunity. *J Clin Invest* 2015; **125**: 2228-2233 [PMID: 25893595 DOI: 10.1172/JCI78088]
 - 93 **Goris A**, Liston A. The immunogenetic architecture of autoimmune disease. *Cold Spring Harb Perspect Biol* 2012; **4**: a007260 [PMID: 22383754 DOI: 10.1101/cshperspect.a007260]
 - 94 **Liblau R**, Tourmier-Lasserve E, Maciazek J, Dumas G, Siffert O, Hashim G, Bach MA. T cell response to myelin basic protein epitopes in multiple sclerosis patients and healthy subjects. *Eur J Immunol* 1991; **21**: 1391-1395 [PMID: 1710565 DOI: 10.1002/eji.1830210610]

- 95 **Allan JC**, Craig PS. Coproantigens in taeniasis and echinococcosis. *Parasitol Int* 2006; **55** Suppl: S75-S80 [PMID: 16337428 DOI: 10.1016/j.parint.2005.11.010]
- 96 **Vandenbroeck K**. Cytokine gene polymorphisms and human autoimmune disease in the era of genome-wide association studies. *J Interferon Cytokine Res* 2012; **32**: 139-151 [PMID: 22191464 DOI: 10.1089/jir.2011.0103]
- 97 **Papp KA**, Leonardi C, Menter A, Ortonne JP, Krueger JG, Kricorian G, Aras G, Li J, Russell CB, Thompson EH, Baumgartner S. Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. *N Engl J Med* 2012; **366**: 1181-1189 [PMID: 22455412 DOI: 10.1056/NEJMoa1109017]
- 98 **Bennett CL**, Christie J, Ramsdell F, Brunkow ME, Ferguson PJ, Whitesell L, Kelly TE, Saulsbury FT, Chance PF, Ochs HD. The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. *Nat Genet* 2001; **27**: 20-21 [PMID: 11137993 DOI: 10.1038/83713]
- 99 **Finnish-German APECED Consortium**. An autoimmune disease, APECED, caused by mutations in a novel gene featuring two PHD-type zinc-finger domains. *Nat Genet* 1997; **17**: 399-403 [PMID: 9398840 DOI: 10.1038/ng1297-399]
- 100 **Fisher GH**, Rosenberg FJ, Straus SE, Dale JK, Middleton LA, Lin AY, Strober W, Lenardo MJ, Puck JM. Dominant interfering Fas gene mutations impair apoptosis in a human autoimmune lymphoproliferative syndrome. *Cell* 1995; **81**: 935-946 [PMID: 7540117 DOI: 10.1016/0092-8674(95)90013-6]
- 101 **Mills KH**. TLR-dependent T cell activation in autoimmunity. *Nat Rev Immunol* 2011; **11**: 807-822 [PMID: 22094985 DOI: 10.1038/nri3095]
- 102 **Root-Bernstein R**, Fairweather D. Complexities in the relationship between infection and autoimmunity. *Curr Allergy Asthma Rep* 2014; **14**: 407 [PMID: 24352912 DOI: 10.1007/s11882-013-0407-3]
- 103 **Serafini B**, Rosicarelli B, Franciotta D, Magliozzi R, Reynolds R, Cinque P, Andreoni L, Trivedi P, Salvetti M, Faggioni A, Aloisi F. Dysregulated Epstein-Barr virus infection in the multiple sclerosis brain. *J Exp Med* 2007; **204**: 2899-2912 [PMID: 17984305 DOI: 10.1084/jem.20071030]
- 104 **Ben-Ami Shor D**, Harel M, Eliakim R, Shoenfeld Y. The hygiene theory harnessing helminths and their ova to treat autoimmunity. *Clin Rev Allergy Immunol* 2013; **45**: 211-216 [PMID: 23325330 DOI: 10.1007/s12016-012-8352-9]
- 105 **Ochoa-Repáraz J**, Mielcarz DW, Ditrio LE, Burroughs AR, Begum-Haque S, Dasgupta S, Kasper DL, Kasper LH. Central nervous system demyelinating disease protection by the human commensal *Bacteroides fragilis* depends on polysaccharide A expression. *J Immunol* 2010; **185**: 4101-4108 [PMID: 20817872 DOI: 10.4049/jimmunol.1001443]
- 106 **Belkaid Y**, Hand TW. Role of the microbiota in immunity and inflammation. *Cell* 2014; **157**: 121-141 [PMID: 24679531 DOI: 10.1016/j.cell.2014.03.011]
- 107 **Steinman RM**, Turley S, Mellman I, Inaba K. The induction of tolerance by dendritic cells that have captured apoptotic cells. *J Exp Med* 2000; **191**: 411-416 [PMID: 10662786]
- 108 **Yurasov S**, Wardemann H, Hammersen J, Tsuiji M, Meffre E, Pascual V, Nussenzweig MC. Defective B cell tolerance checkpoints in systemic lupus erythematosus. *J Exp Med* 2005; **201**: 703-711 [PMID: 15738055 DOI: 10.1084/jem.20042251]
- 109 **Bluestone JA**, Tang Q, Sedwick CE. T regulatory cells in autoimmune diabetes: past challenges, future prospects. *J Clin Immunol* 2008; **28**: 677-684 [PMID: 18716861 DOI: 10.1007/s10875-008-9242-z]
- 110 **Banchereau J**, Pascual V. Type I interferon in systemic lupus erythematosus and other autoimmune diseases. *Immunity* 2006; **25**: 383-392 [PMID: 16979570 DOI: 10.1016/j.immuni.2006.08.010]
- 111 **Girelli G**, Teggi A, Perrone MP, Di Vico B, Gandolfo GM, De Rosa F. Anti-erythrocyte autoimmunization in hydatid disease. *Int J Clin Lab Res* 1993; **23**: 113-115 [PMID: 8518413 DOI: 10.1007/BF02592293/]
- 112 **De Rosa FG**, Amoroso A, Teggi A, Paparo SB, Franchi C, Ferri GM, Caccavo D, Afeltra A. Anti-neutrophil cytoplasmic antibodies in echinococcus granulosus hydatid disease. *Hum Immunol* 2001; **62**: 1122-1126 [PMID: 11600219 DOI: 10.1016/S0198-8859(01)00309-3]
- 113 **Aslan M**, Saribas S, Polat E, Cakan H, Yuksel P, Zengin K, Arkan S, Oner YA, Torun MM and Kocazeybek B. Can cystic echinococcosis trigger autoimmunity? *African J Microbiol Research* 2009; **3**: 787-790 [DOI: 10.5897/AJMR]
- 114 **Romani L**. Parasites and autoimmunity: the case of fungi. *Autoimmun Rev* 2008; **8**: 129-133 [PMID: 18703172 DOI: 10.1016/j.autrev.2008.07.004]
- 115 **Garcia Fernandez MI**, Ceccarelli D, Muscatello U. Use of the fluorescent dye 10-N-nonyl acridine orange in quantitative and location assays of cardiolipin: a study on different experimental models. *Anal Biochem* 2004; **328**: 174-180 [PMID: 15113694 DOI: 10.1016/j.ab.2004.01.020]
- 116 **Lodish H**, Berk A, Kaiser C, Kreiger M, Scott M, Bretscher A. *Molecular Cell Biology* 5th ed. New York: W.H. Freeman & Company, 2008: 429
- 117 **Pordeus V**, Szyper-Kravitz M, Levy RA, Vaz NM, Shoenfeld Y. Infections and autoimmunity: a panorama. *Clin Rev Allergy Immunol* 2008; **34**: 283-299 [PMID: 18231878 DOI: 10.1007/s12016-007-8048-8]
- 118 **Gause WC**, Wynn TA, Allen JE. Type 2 immunity and wound healing: evolutionary refinement of adaptive immunity by helminths. *Nat Rev Immunol* 2013; **13**: 607-614 [PMID: 23827958 DOI: 10.1038/nri3476]
- 119 **Hernandez JL**, Leung G, McKay DM. Cestode regulation of inflammation and inflammatory diseases. *Int J Parasitol* 2013; **43**: 233-243 [PMID: 23058631 DOI: 10.1016/j.ijpara.2012.09.005]
- 120 **Eckert J**, Gemmel MA, Meslin FX, Pawlowski ZS. WHO/OIE Manual on Echinococcus in Humans and Animals: a Public Health Problem of Global Concern. Paris, France: CAB Direct, 2010: 286

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Retrospective Study

Safety and efficacy of ledipasvir/sofosbuvir on hepatitis C eradication in hepatitis C virus/human immunodeficiency virus co-infected patients

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Abstract

AIM

To evaluate the safety and efficacy of ledipasvir/sofosbuvir on hepatitis C eradication in patients with hepatitis C virus (HCV)/human immunodeficiency virus (HIV) co-infection in an urban HIV clinic.

METHODS

A retrospective cohort study of 40 subjects co-infected with HIV-1 and HCV treated with the fixed-dose combination of ledipasvir and sofosbuvir for 12 wk from 2014 to 2016. All patients included were receiving antiretroviral therapy (ART) with HIV RNA values of 100 copies/mL or fewer regardless of baseline HCV RNA level. The primary end point was a sustained virologic response of HCV at 12 wk (SVR12) after the end of therapy.

RESULTS

Of the 40 patients enrolled, 55% were black, 22.5% had been previously treated for HCV, and 25% had

cirrhosis. The patients were on a wide range of ART. Overall, 39 patients (97.5%) had a SVR 12 after the end of therapy, including rates of 97.1% in patients with HCV genotype 1a and 100% in those with HCV genotype 1b. One patient with HCV genotype 3a was included and achieved SVR12. Rates of SVR12 were similar regardless of previous treatment or the presence of compensated cirrhosis. Only 1 patient experienced relapse at week 12 following treatment and deep sequencing didn't reveal any resistance associated mutation in the NS5A or NS5B region. Interestingly, 7 (17.5%) patients who were adherent to ART experienced HIV viral breakthrough which resolved after continuing the same ART regimen. Two (5%) patients experienced HIV-1 virologic rebound due to noncompliance with HIV therapy, which resolved after resuming the same ART regimen. No severe adverse events were observed and no patient discontinued treatment because of adverse events. The most common adverse events included headache (12.5%), fatigue (10%), and diarrhea (2.5%).

CONCLUSION

This retrospective study demonstrated the high rates of SVR12 of ledipasvir/sofosbuvir on HCV eradication in patients co-infected with HCV and HIV, regardless of HCV baseline levels, HCV treatment history or cirrhosis condition. The oral combination of ledipasvir/sofosbuvir represents a safe and well tolerated HCV treatment option that does not require modification for many of the common HIV ART. Occasional HIV virologic rebound occurred but later resolved without the need to change ART.

Key words: Hepatitis C; Human immunodeficiency virus; Ledipasvir; Sofosbuvir

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Core tip: This is a retrospective study to evaluate the safety and efficacy of ledipasvir/sofosbuvir on hepatitis C eradication in patients with hepatitis C virus (HCV) and human immunodeficiency virus (HIV) co-infection in an urban HIV clinic. It demonstrated the high rates of SVR12 of ledipasvir/sofosbuvir on HCV eradication in patients co-infected with HCV and HIV, regardless of HCV baseline levels, HCV treatment history or cirrhosis condition. The oral combination of ledipasvir/sofosbuvir represents a safe and well tolerated HCV treatment option that does not require modification for many of the common HIV antiretroviral therapy (ART). Occasional HIV virologic rebound occurred but later resolved without the need to change ART.

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INTRODUCTION

More than 185 million people around the world are infected with the hepatitis C virus (HCV), 350000 of whom die each year^[1,2]. Human immunodeficiency virus (HIV) and HCV have common routes of transmission, and it is estimated that 4-5 million persons out of the 185 million infected by HCV are also co-infected by HIV. On the other hand, up to 30% of HIV positive patients are infected with HCV^[2,3]. There is increasing evidence that HCV coinfection has a harmful effect on the progression of HIV infection with increased risk of mortality^[4]. Liver disease has become a major cause of morbidity and mortality in HIV-infected persons.

Sustained viral response (SVR) (equivalent to eradication of HCV) after administering anti-HCV therapy is associated with improved survival and reduced liver decompensation in patients with chronic hepatitis C with HIV infection^[5,6]. It may also decrease the progression of HIV infection and mortality not related to liver disease^[7]. The mainstay of therapy over the last two decades involved a combination of interferon α and ribavirin (RBV). SVR rates with pegylated interferon and RBV were very low, averaging between 40% and 50% and the treatment duration required is long, ranging from 24 to 48 wk^[1]. In addition, peginterferon has many side effects and contraindications. Many patients with HIV infection are unwilling to take interferon. The availability of an effective HCV interferon free regimen is highly needed for the management of hepatitis C in HIV infected patients.

In recent years, the management of chronic hepatitis C has been revolutionized by the development of direct-acting antiviral agents (DAAs) which significantly improved rates of cure in chronic HCV infection. Ledipasvir is an inhibitor of nonstructural protein 5A (NS5A), which has an important role in HCV RNA replication^[8]. Sofosbuvir (SOF), a uridine nucleotide analog prodrug, was approved by the US FDA in December 2013. The active metabolite of SOF, is incorporated by the NS5B polymerase into HCV RNA, resulting in chain termination^[3]. The fixed-dose combination of ledipasvir and sofosbuvir has demonstrated minimal toxicities and high efficacy, with an overall SVR of over 91%, in patients infected with HCV genotype 1, without the need for either interferon or RBV^[8-10]. Osinusi *et al*^[11] for the first time, reported that the combination of ledipasvir and sofosbuvir was associated with SVR rate of 98% in patients co-infected with HCV genotype 1 and HIV in a phase 2 study. Later, a larger phase 3 trial (ION-4 study) demonstrated that 12 wk of treatment with ledipasvir/sofosbuvir resulted in a SVR rate of 96% in patients who were co-infected with HIV and HCV genotype 1 or 4^[12]. Harvoni, the fixed dose combination of ledipasvir and sofosbuvir, became the first approved once daily Single-tablet-regimen (STR) for treatment of chronic HCV in HIV positive patients in Nov 2015. This combination may have additional mental health benefits in HIV/HCV co-infected patients^[13].

Currently, there are few published data on the experience with this newly approved combination of ledi-

Table 1 Demographic characteristics of the patients at baseline *n* (%)

Characteristic	Ledipasvir/sofosbuvir for 12 wk (<i>n</i> = 40)
Median age (IQR) - yr	53 (51-57)
Male sex	25 (62.5)
Race ¹	
White	13 (32.5)
Black	22 (55.0)
Asian	1 (2.5)
Other or unknown	4 (10.0)
Mean body-mass index (IQR) ²	26.2 (22.7-28.7)
Smoking	13 (32.5)
HCV genotype	
1a	34 (85.0)
1b	5 (12.5)
3a	1 (2.5)
Baseline HCV RNA (IQR), log ₁₀ IU/mL	6.3 (6.0-6.6)
HCV RNA > 6 million IU/mL	5 (12.5)
Cirrhosis	10 (25.0)
Baseline creatinine, mean (range), mg/dL	0.95 (0.56-1.48)
Baseline eGFR, mean (range), mL/min	90.0 (52-134)
CD4, cells/mm ³	
< 200	1 (2.5)
200-350	7 (17.5)
> 350	32 (80)
Mean CD4 ⁺ cell count (IQR), cells/μL	638 (366-857)
Antiviral regimen	40 (100)
HCV treatment history	
No previous treatment	31 (77.5)
Previous treatment	9 (22.5)

¹Self-reported; ²Calculated as weight in kilograms divided by height in meters squared. BMI: Body mass index; eGFR: Estimated glomerular filtration rate; HCV: Hepatitis C virus; IQR: Interquartile range.

pasvir/sofosbuvir in HCV/HIV co-infected patients. Here, we reported a single-center, retrospective study evaluating the safety and efficacy of this combination on HCV eradication in the patients co-infected with HCV and HIV with or without previous treatment for HCV.

MATERIALS AND METHODS

Study design and setting

This was a retrospective cohort study. All of the research reviews were conducted under protocols approved by the institutional independent ethics committee and all data were collected and analyzed in a Health Insurance Portability and Accountability Act-compliant manner to ensure patient privacy and data integrity. The study was conducted in Sunshine Care Center (Florida Department of Health in Orange County, Orlando, FL), an urban HIV clinic in Orlando.

Subjects

Patients older than 18 years diagnosed as HIV/HCV co-infection at Sunshine Care Center between 2014 and 2016 and treated with the fixed dose combination of ledipasvir/sofosbuvir for 12 wk were included. Charts were reviewed and data were collected by a trained internal medicine resident. The presence of cirrhosis was determined by liver biopsy with a Metavir score of F4; or

a score of more than 12.5 kPa on transient elastography testing (Fibroscan); or Radiological imaging consistent with cirrhosis.

For each patient included in the study, the demographic data were collected through manual chart review, including age, race, sex, body-mass index (BMI), smoking history, HCV genotype, and medical history (Table 1).

Efficacy and safety assessments

The primary efficacy end point was sustained virologic response (HCV RNA level < 15 IU/mL by real-time HCV assay) at 12 wk after treatment completion (SVR12) among all patients enrolled in the study.

Pre-treatment, during treatment, and post-treatment data of the standard laboratory testing (complete blood count (CBC), levels of albumin, bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen, creatinine) and measurements of plasma HCV RNA and HIV-1 RNA levels, along with evaluations of adherence were collected. Plasma HCV RNA levels were measured using the real-time HCV assay (Abbott), with the Lower Limit of Quantitation (LLOQ) of 15 IU/mL. Plasma HIV RNA levels were measured at all points using reverse transcription polymerase chain reaction (real-time HIV assay), with an LLOQ of 40 copies/mL. Adherence to ledipasvir and sofosbuvir was measured by pill counts and patient self-report. All adverse events were recorded and graded according to the NIAID Division of AIDS toxicity table (version 1.0 2009 clarification).

Definitions

Hepatitis C viral relapse was defined as an HCV RNA level higher than the LLOQ at any posttreatment point after having an HCV RNA level lower than the LLOQ at the end of treatment. Hepatitis C viral breakthrough was defined as an HCV RNA level at the LLOQ or higher during treatment after having previously had an HCV RNA level lower than the LLOQ while taking study drugs, confirmed with 2 consecutive values. HIV viral breakthrough was defined as an HIV RNA level at the LLOQ or higher during treatment after having previously had an HIV RNA level lower than the LLOQ while taking ART, confirmed with 2 consecutive values. Patients with plasma HIV-1 RNA levels of 400 copies per milliliter or higher at two or more consecutive post-baseline visits at least 2 wk apart were considered to have HIV-1 virologic rebound.

Deep sequencing

Deep sequencing of the HCV NS5A and NS5B regions was performed only for the patient with virologic failure, from samples collected at the time of virologic failure, using DDL (DDL Diagnostics Laboratory). Variants that were present in at least 1% of the viral population were reported.

Statistical analysis

We calculated the proportion of patients who had a

Table 2 Antiviral regimen

Antiviral regimen	n (%)
Efavirenz-emtricitabine-tenofovir DF	1 (2.5)
Tivicay-emtricitabine-tenofovir DF	1 (2.5)
Rilpivirine-emtricitabine-tenofovir DF	5 (12.5)
Raltegravir- Rilpivirine-emtricitabine-tenofovir DF	2 (5)
Raltegravir-emtricitabine-tenofovir DF	6 (15)
Ritonavir- Raltegravir-emtricitabine-tenofovir DF	1 (2.5)
Dolutegravir-emtricitabine-tenofovir DF	1 (2.5)
Raltegravir-telaprevir	4 (10)
Abacavir-dolutegravir-lamivudine	8 (20)
Abacavir-etravirine-lamivudine	1 (2.5)
Darunavir-ritonavir-etravirine-raltegravir	3 (7.5)
Abacavir-lamivudine-darunavir-ritonavir	3 (7.5)
Abacavir-lamivudine-darunavir-ritonavir-etravirine-raltegravir	1 (2.5)
Elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide	3 (7.5)

DF: Disoproxil fumarate.

sustained virologic response along with exact two-sided 95%CI using the Clopper-Pearson method. Statistical differences were analyzed by χ^2 tests for categorical variables and *t*-test for continuous variables with significance defined as a *P* value less than 0.05.

RESULTS

Study patients

A total of 40 patients were enrolled. Eighty-five percent of patients were infected with HCV genotype 1a, 12.5% with HCV genotype 1b, and 2.5% with HCV genotype 3a (Table 1). Overall, 55% of patients were black, 62.5% were male, 25% had compensated cirrhosis, and 22.5% had received previous unsuccessful treatment for HCV. Among the 10 patients with cirrhosis, the mean baseline albumin level was 4.3 g per deciliter, the mean platelet count was 110940 per microliter, the mean Bilirubin level was 1.0 milligrams per deciliter (mg/dL), the mean ALP level was 101 units per liter (U/L), the mean ALT level was 89 U/L, and the mean AST level was 67 U/L. Nine patients received previous treatments for HCV with pegylated interferon (peginterferon) plus ribavirin. All patients were receiving ART with a wide range of regimen (Table 2).

Efficacy

Among the 40 patients who were enrolled and treated, 39 [97.5%; 95% confidence interval (CI), 90 to 100] had a sustained virologic response 12 wk after the end of therapy (Table 3). The rates of response at 12 wk were similar in patients with genotype 1a (97%) and those with 1b (100%), in men (96%) and women (100%), in black patients (100%) and other races (94.4%), in patients who had undergone previous treatment (100%) and those who had not (96.8%), in patients with cirrhosis (100%) and those without cirrhosis (96.7%).

Only 1 patient did not achieve SVR12 and experienced

Table 3 Response during and after therapy

Response	Ledipasvir-Sofosbuvir for 12 wk (n = 40), n (%)
HCV RNA < LLOQ ¹	
During therapy period	
At wk 4	34 (78.2)
At wk 12	40 (100)
After end of therapy	
At wk 4	40 (100)
At wk 12 ²	39 (97.5)
HCV viral breakthrough	0 (0)
HCV viral relapse	1 (2.5)
HIV viral breakthrough	7 (17.5)
HIV virologic rebound	2 (5)

¹LLOQ denotes lower limit of quantification (HCV RNA in serum, < 15 copies per milliliter HIV RNA in serum, < 40 copies per milliliter).

²A sustained virologic response 12 wk after the end of therapy was the primary end point. SVR: Sustained viral response.

relapse by week 12 after treatment completion. This was a 53-year-old white male, with HCV genotype 1a infection and stage 1 liver disease. The baseline HCV viral load was 11370594 IU/mL as determined by real-time PCR assay. The medications that he received against HIV infection included raltegravir, etravirine, ritonavir and darunavir. HCV viral suppression was achieved by week 8 with viral load lower than the LLOQ, which was maintained through 12 wk. However, HCV viral load increased to 7043 IU/mL at week 12 after treatment completion and was 7165187 at week 16 after treatment completion. Deep sequencing failed to reveal any mutation was seen in the NS5A or NS5B region.

Changes in liver and renal function

Levels of ALT and AST became normal rapidly with treatment (Figure 1A). There were no significant changes in estimated GFR or serum creatinine levels over time (Figure 1B and C). No participants were identified as having a treatment-emergent eGFR less than 50 mL/min or a decrease in eGFR (mL/min) greater than 25%.

Changes in HIV parameters

The mean CD4⁺ cell count at baseline was 638 cells per microliter; the CD4⁺ count was under 200 cells per microliter in 1 patient and under 350 cells per microliter in 7 patients. There were no significant changes in CD4 cell counts with treatment (Figure 1D).

Two patients experienced HIV-1 virologic rebound. One had missed 2 wk ART (emtricitabine/rilpivirine/tenofovir DF) and the other had missed 5 d of ART (emtricitabine/tenofovir DF/raltegravir). They continued the same regimen and the HIV viral load was less than 20 copies/mL by the next visit (4 wk later). Moreover, 7 patients experienced HIV breakthrough, a transient increase in HIV viral load (HIV-1 RNA \geq 40 copies/mL) while in the study. All of them denied non-compliance with ART. They continued the same regimen and the HIV viral load was less than 40 copies/mL 4 to 8 wk later. All of these 9 patients achieved

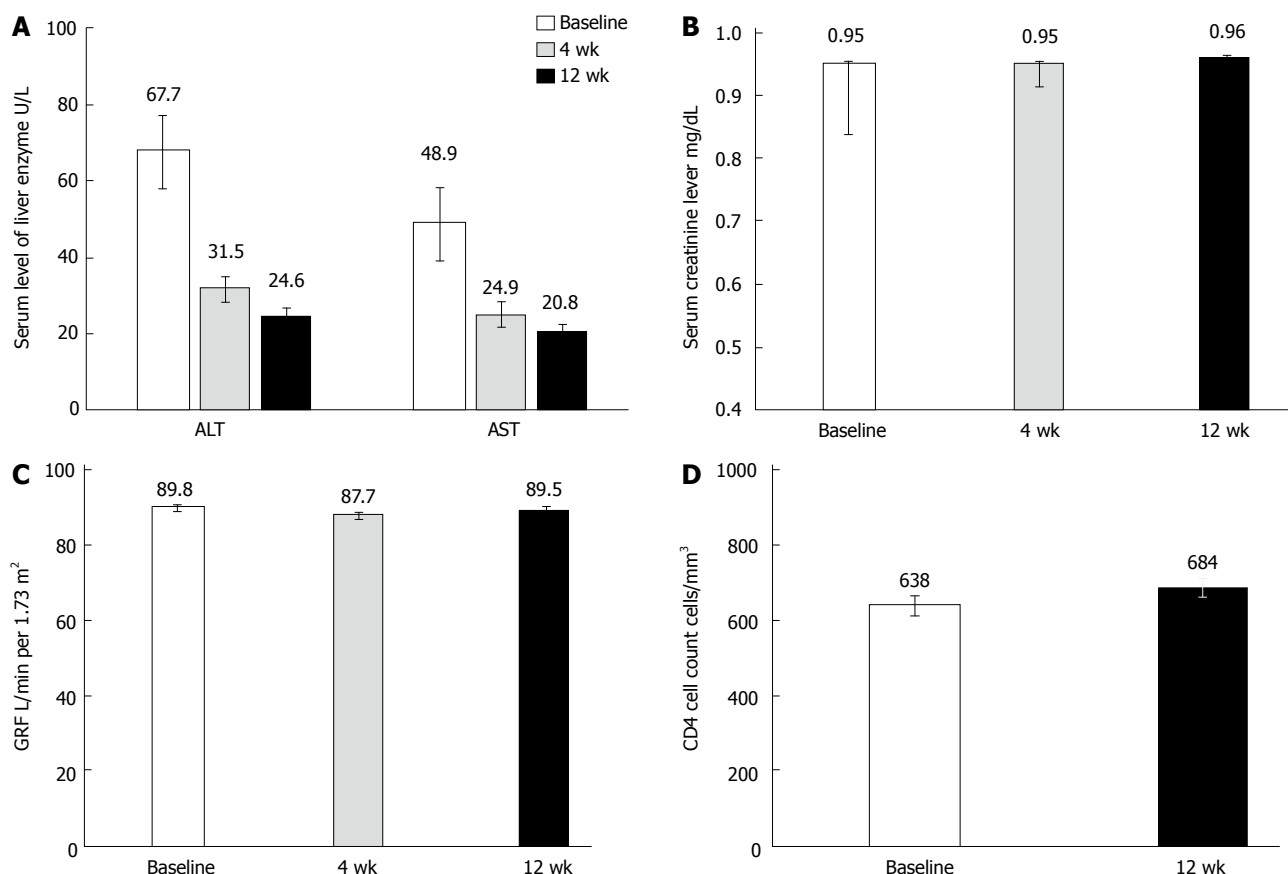


Figure 1 Lab changes during treatment. A: Changes in liver function tests; B: Changes in serum creatinine level; C: Changes in GFR level; D: Changes in CD4 cell count.

SVR12 for HCV treatment.

Adverse events

There were no deaths or serious adverse events observed in this study. The most common adverse events were mild to moderate headache (12.5%), fatigue (10%), and diarrhea (2.5%). Symptoms resolved while the patient was receiving study drug.

Adherence

Adherence to ledipasvir and sofosbuvir, as measured by pill counts, was high over the course of treatment. Ninety-five percent of all participants had no missed doses. Five percent of patients missed 1 to 4 doses of study drug, for an adherence rate greater than 95%. As determined by pill count at the end of study, the participant who experienced HCV viral relapse by week 12 after treatment completion reported no missed doses.

DISCUSSION

In this retrospective study, the combination of ledipasvir and sofosbuvir was associated with a high rate of SVR (97.5%) in HIV and HCV co-infected patients, comparable with SVR rates observed in the previous clinical trials^[11-13]. Our study included HCV treatment-naïve (77.5%) and

treatment-experienced (22.5%) patients, including patients with compensated cirrhosis (25%). Consistent with the previous reports^[11,12], HCV treatment history, baseline HCV RNA levels, and cirrhosis didn't appear to have any effect on SVR12 rates. All 9 treatment experienced patients and 30 of 31 treatment naïve patients achieved SVR, regardless of HCV baseline levels. One patient with HCV 3a genotype was also allowed to enroll in the study and successfully achieved SVR12. In the recent ION 4 study, black patients with HCV and HIV co-infection were reported to have lower rates of SVR compared to non-black patients who received 12 wk treatment of ledipasvir/sofosbuvir^[12]. However, no differences in efficacy were observed in patients when stratified by race in our study. Using data from the three open-label ION clinical trials, Wilder *et al.*^[14] evaluated the efficacy of ledipasvir/sofosbuvir in 308 black patients. Consistent with our result, they found that an once daily dosage of ledipasvir/sofosbuvir was similarly effective in black and non-black patients with genotype 1 HCV infection. In the 1 participant who experienced relapse, HCV sequencing data didn't detect any mutation in the NS5A or NS5B region at the time of relapse and the patient was adherent to his medications, suggesting that the underlying mechanism contributing to the resistance to this regimen is unknown and needs future investigation.

All patients enrolled in this study were receiving

an antiretroviral regimen for HIV-1 with evidence of HIV-1 viral suppression to a level less than 100 copies per milliliter. The main strength of this study was that the patients were on a wide range of antiretrovirals, including complex antiretroviral regimens that contained drugs from 3 or more antiretroviral classes. Drug-drug interactions between certain directly acting antiviral agents such as boceprevir, telaprevir, and antiretrovirals could result in adverse events or antiretroviral failures, restricting the wider use of these medications in patients with HIV^[15,16]. Although Ledipasvir-sofosbuvir has limited potential for clinically significant drug interactions with most antiretroviral agents^[17], the results from the phase 1^[17] and 3^[12] evaluations suggested potential drug interaction between ledipasvir/sofosbuvir and tenofovir resulting in increased exposure of tenofovir. Four patients developed treatment-emergent worsening of renal function which might be related to increased exposure of tenofovir^[12]. In our study, evaluation of renal function didn't reveal significant changes in GFRs and serum creatinine levels throughout this study and no patients taking tenofovir were required to modify HIV treatment due to tenofovir-induced complications. In the previous study, patients taking ritonavir-boosted HIV-1 protease inhibitors or cobicistat-boosted elvitegravir with tenofovir disoproxil fumarate were excluded, so the safety of this HCV combination in patients with HIV-1 infection who are receiving these antiretroviral regimens is unknown^[12]. Interestingly, 11 patients enrolled in this study were on ritonavir-boosted or cobicistat-boosted ART and no severe adverse effects were noticed with SVR12 rates of 91.0% (the patient who experienced relapse was receiving the combination of darunavir-ritonavir-etravirine-raltegravir for ART). Thus, ledipasvir/sofosbuvir treatment represents a safe HCV treatment option that does not require modification for many of the common antiretroviral regimens.

In our study, ledipasvir/sofosbuvir treatment in HIV-HCV-coinfected patients did not compromise HIV control. CD4 cell counts remained stable and HIV RNA remained suppressed for the majority of participants throughout the study. Seven patients who were adherent to the medications experienced transient mild HIV viral breakthrough with maximum HIV RNA less than 250 copies. The viral breakthrough resolved spontaneously 4 to 8 wk after the patients were continuing the same ART regimen. HIV viral rebound documented in 2 participants was associated with nonadherence to antiretroviral treatment, which also resolved after resuming the same ART treatment.

In this study, there were no deaths, medication discontinuations, or severe adverse events attributable to ledipasvir/sofosbuvir treatment. Most adverse events associated with combined ledipasvir and sofosbuvir in participants co-infected with HCV and HIV were mild.

In conclusion, excellent treatment outcomes among our cohort of HIV/HCV co-infected patients were achieved with the FDA approved combination of ledipasvir/sofosbuvir for HCV. The main strength of this study was

that a broad range of antiretrovirals were included in this study which demonstrated that ledipasvir/sofosbuvir was generally well tolerated when coadministered with a broad range of ART. Larger studies are required to further understand the efficacy and safety of the combination of ledipasvir/sofosbuvir in HIV/HCV co-infected patients.

COMMENTS

Background

Hepatitis C virus (HCV) coinfection has a harmful effect on the progression of human immunodeficiency (HIV) infection with increased risk of mortality. In recent years, the management of chronic hepatitis C has been revolutionized by the development of direct-acting antiviral agents (DAAs) which significantly improved rates of cure in chronic HCV infection.

Research frontiers

The fixed dose combination of ledipasvir and sofosbuvir demonstrated high SVR rate in patients infected with HCV and recently became the first approved once daily single-tablet-regimen for treatment of chronic HCV in HIV positive patients. Currently, there are few published data on the experience with this newly approved combination of ledipasvir/sofosbuvir in HCV/HIV co-infected patients. The drug interaction is always a safety concern while treating HCV/HIV co-infected patients.

Innovations and breakthroughs

The authors conducted a single-center, retrospective study evaluating the safety and efficacy of the combination of ledipasvir/sofosbuvir on HCV eradication in the patients co-infected with HCV and HIV with or without previous treatment for HCV. Overall, the rate of SVR12 was 97.5% and only 1 (2.5%) patient experienced relapse at week 12 following treatment. No severe adverse events were observed and no patient discontinued treatment because of adverse events.

Applications

The results demonstrated that this combination represents a safe and well tolerated HCV treatment option that does not require modification for many of the common HIV ART.

Terminology

SVR: Sustained viral response. SVR is specific to hepatitis C and is the absence of HCV RNA for 12 wk after the cessation of treatment.

Peer-review

Clearly written and stylish manuscript. The approach is not very original (in the last years several papers regarding the efficacy of DDA in real life settings have been published) but since in this subgroup of patients there are few publications, it is still interesting.

REFERENCES

- 1 **Lam BP**, Jeffers T, Younoszai Z, Fazel Y, Younoszi ZM. The changing landscape of hepatitis C virus therapy: focus on interferon-free treatment. *Therap Adv Gastroenterol* 2015; **8**: 298-312 [PMID: 26327920 DOI: 10.1177/1756283X15587481]
- 2 **Puoti M**, Panzeri C, Rossotti R, Baiguera C. Efficacy of sofosbuvir-based therapies in HIV/HCV infected patients and persons who inject drugs. *Dig Liver Dis* 2014; **46** Suppl 5: S206-S211 [PMID: 25458781 DOI: 10.1016/j.dld.2014.09.027]
- 3 **McQuaid T**, Savini C, Seyedkazemi S. Sofosbuvir, a Significant Paradigm Change in HCV Treatment. *J Clin Transl Hepatol* 2015; **3**: 27-35 [PMID: 26357632 DOI: 10.14218/JCTH.2014.00041]
- 4 **Puoti M**, Rossotti R, Travi G, Panzeri C, Morreale M, Chiari E, Cocca G, Orso M, Moioli MC. Optimizing treatment in HIV/HCV coinfection. *Dig Liver Dis* 2013; **45** Suppl 5: S355-S362 [PMID: 23555362 DOI: 10.1016/j.dld.2013.09.027]

- 24091116 DOI: 10.1016/j.dld.2013.09.001]
- 5 **Limketkai BN**, Mehta SH, Sutcliffe CG, Higgins YM, Torbenson MS, Brinkley SC, Moore RD, Thomas DL, Sulkowski MS. Relationship of liver disease stage and antiviral therapy with liver-related events and death in adults coinfecting with HIV/HCV. *JAMA* 2012; **308**: 370-378 [PMID: 22820790 DOI: 10.1001/jama.2012.7844]
- 6 **Berenguer J**, Alvarez-Pellicer J, Martín PM, López-Aldeguer J, Von Wichmann MA, Quereda C, Mallolas J, Sanz J, Tural C, Bellón JM, González-García J; GESIDA3603/5607 Study Group. Sustained virological response to interferon plus ribavirin reduces liver-related complications and mortality in patients coinfecting with human immunodeficiency virus and hepatitis C virus. *Hepatology* 2009; **50**: 407-413 [PMID: 19575364 DOI: 10.1002/hep.23020]
- 7 **Berenguer J**, Rodríguez E, Miralles P, Von Wichmann MA, López-Aldeguer J, Mallolas J, Galindo MJ, Van Den Eynde E, Téllez MJ, Quereda C, Jou A, Sanz J, Barros C, Santos I, Pulido F, Guardiola JM, Ortega E, Rubio R, Jurdado JJ, Montes ML, Gaspar G, Esteban H, Bellón JM, González-García J; GESIDA HIV/HCV Cohort Study Group. Sustained virological response to interferon plus ribavirin reduces non-liver-related mortality in patients coinfecting with HIV and Hepatitis C virus. *Clin Infect Dis* 2012; **55**: 728-736 [PMID: 22610932 DOI: 10.1093/cid/cis500]
- 8 **Afdhal N**, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, Nahass R, Ghalib R, Gitlin N, Herring R, Lalezari J, Younes ZH, Pockros PJ, Di Bisceglie AM, Arora S, Subramanian GM, Zhu Y, Dvory-Sobol H, Yang JC, Pang PS, Symonds WT, McHutchison JG, Muir AJ, Sulkowski M, Kwo P; ION-2 Investigators. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N Engl J Med* 2014; **370**: 1483-1493 [PMID: 24725238 DOI:10.1056/NEJMoa1316366]
- 9 **Afdhal N**, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, Romero-Gomez M, Zarski JP, Agarwal K, Buggisch P, Foster GR, Bräu N, Buti M, Jacobson IM, Subramanian GM, Ding X, Mo H, Yang JC, Pang PS, Symonds WT, McHutchison JG, Muir AJ, Mangia A, Marcellin P; ION-1 Investigators. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med* 2014; **370**: 1889-1898 [PMID: 24725239 DOI: 10.1056/NEJMoa1316366]
- 10 **Kowdley KV**, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, Shiffman ML, Schiff E, Ghalib R, Ryan M, Rustgi V, Chojkier M, Herring R, Di Bisceglie AM, Pockros PJ, Subramanian GM, An D, Svarovskaia E, Hyland RH, Pang PS, Symonds WT, McHutchison JG, Muir AJ, Pound D, Fried MW; ION-3 Investigators. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med* 2014; **370**: 1879-1888 [PMID: 24720702 DOI: 10.1056/NEJMoa1402355]
- 11 **Osinusi A**, Townsend K, Kohli A, Nelson A, Seamon C, Meissner EG, Bon D, Silk R, Gross C, Price A, Sajadi M, Sidharthan S, Sims Z, Herrmann E, Hogan J, Teferi G, Talwani R, Proschan M, Jenkins V, Kleiner DE, Wood BJ, Subramanian GM, Pang PS, McHutchison JG, Polis MA, Fauci AS, Masur H, Kottitil S. Virologic response following combined ledipasvir and sofosbuvir administration in patients with HCV genotype 1 and HIV co-infection. *JAMA* 2015; **313**: 1232-1239 [PMID: 25706232 DOI: 10.1001/jama.2015.1373]
- 12 **Naggie S**, Cooper C, Saag M, Workowski K, Ruane P, Towner WJ, Marks K, Luetkemeyer A, Baden RP, Sax PE, Gane E, Santana-Bagur J, Stamm LM, Yang JC, German P, Dvory-Sobol H, Ni L, Pang PS, McHutchison JG, Stedman CA, Morales-Ramirez JO, Bräu N, Jayaweera D, Colson AE, Tebas P, Wong DK, Dieterich D, Sulkowski M; ION-4 Investigators. Ledipasvir and Sofosbuvir for HCV in Patients Coinfecting with HIV-1. *N Engl J Med* 2015; **373**: 705-713 [PMID: 26196665 DOI: 10.1056/NEJMoa1501315]
- 13 **Tang LS**, Masur J, Sims Z, Nelson A, Osinusi A, Kohli A, Kattakuzhy S, Polis M, Kottitil S. Safe and effective sofosbuvir-based therapy in patients with mental health disease on hepatitis C virus treatment. *World J Hepatol* 2016; **8**: 1318-1326 [PMID: 27872683 DOI: 10.4254/wjh.v8.i31.1318]
- 14 **Wilder JM**, Jeffers LJ, Ravendhran N, Shiffman ML, Poulos J, Sulkowski MS, Gitlin N, Workowski K, Zhu Y, Yang JC, Pang PS, McHutchison JG, Muir AJ, Howell C, Kowdley K, Afdhal N, Reddy KR. Safety and efficacy of ledipasvir-sofosbuvir in black patients with hepatitis C virus infection: A retrospective analysis of phase 3 data. *Hepatology* 2016; **63**: 437-444 [PMID: 26547499 DOI: 10.1002/hep.28334]
- 15 **Sulkowski MS**, Sherman KE, Dieterich DT, Bsharat M, Mahnke L, Rockstroh JK, Gharakhanian S, McCallister S, Henshaw J, Girard PM, Adiwijaya B, Garg V, Rubin RA, Adda N, Soriano V. Combination therapy with telaprevir for chronic hepatitis C virus genotype 1 infection in patients with HIV: a randomized trial. *Ann Intern Med* 2013; **159**: 86-96 [PMID: 23685940 DOI: 10.7326/0003-4819-159-2-201307160-00654]
- 16 **Sulkowski M**, Pol S, Mallolas J, Fainboim H, Cooper C, Slim J, Rivero A, Mak C, Thompson S, Howe AY, Wenning L, Sklar P, Wahl J, Greaves W; P05411 study investigators. Boceprevir versus placebo with pegylated interferon alfa-2b and ribavirin for treatment of hepatitis C virus genotype 1 in patients with HIV: a randomised, double-blind, controlled phase 2 trial. *Lancet Infect Dis* 2013; **13**: 597-605 [PMID: 23768747 DOI: 10.1016/S1473-3099(13)70149-X]
- 17 Harvoni (ledipasvir-sofosbuvir) tablets: U.S. prescribing information. Foster City, CA: Gilead Sciences; 2015. Available from: URL: http://www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/harvoni/harvoni_pi.pdf

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