Clinical Microbiology and Infection 23 (2017) 935–940

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Guidelines

Recommendations for screening, monitoring, prevention, prophylaxis and therapy of hepatitis B virus reactivation in patients with haematologic malignancies and patients who underwent haematologic stem cell transplantation—a position paper

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ARTICLE INFO

Article history:
Received 7 March 2017
Received in revised form
15 June 2017
Accepted 17 June 2017
Available online 29 June 2017

Editor: L. Leibovici

Keywords:
Haematologic malignancies
Haematologic stem cell transplantation
HBV infection
HBV prophylaxis
HBV reactivation
Hepatitis B virus

ABSTRACT

Scope: Hepatitis B virus (HBV) infection reactivation is associated with high morbidity and mortality in patients with haematologic malignancy and/or haematopoietic stem cell transplantation (HSCT). However, information on this issue is limited. The scope of this position paper is to provide recommendations on HBV screening, monitoring, prophylaxis, treatment and vaccination in the patients described above.
Methods: These recommendations were developed from one meeting of experts attended by different Italian scientific societies as well as from a systematic literature review (of articles published through December 31, 2016) on HBV infection in haematologic patients and in patients who underwent haematopoietic stem cell transplantation published in the same issue of the journal. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used to assess each recommendation's quality.
Questions addressed: These recommendations provide the answers to the following questions: (a) HBV screening and monitoring: Who should be screened before chemotherapy? Which screening tests should be used? Should HBV-DNA detection be used to monitor HBV reactivation before starting antivirals? What is the best timeline to monitor HBV reactivation? (b) Prophylaxis in HBsAg-positive patients: Which antiviral drugs should be used to treat HBsAg-positive patients? How long should antiviral prophylaxis be provided to HBsAg-positive patients? (c) Prophylaxis in patients with resolved HBV infection: Which patients with resolved HBV infection should receive antiviral prophylaxis? Which antiviral drug should be used? How long should antiviral prophylaxis be provided? (d) HBV infection management strategy in autologous (auto-HSCT) and allogeneic HSCT (allo-HSCT): Which HSCT

DOI of original article: http://dx.doi.org/10.1016/j.cmi.2017.06.024.
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http://dx.doi.org/10.1016/j.cmi.2017.06.023

recipients should receive antiviral prophylaxis? Which antiviral drug should be used? How long should antiviral prophylaxis be provided? (e) Choice of antiviral drugs in the treatment of HBV reactivation: Should third-generation anti-HBV drugs be preferred to first- or second-generation antiviral drugs in the treatment of HBV reactivation with or without hepatitis flare in haematologic patients? (f) Immunization against HBV in patients with haematologic malignancies and/or patients who underwent HSCT: Should these patients be vaccinated? Which HBV vaccination schedule should be adopted?
Recommendations: Haematologic patients should be screened for hepatitis B surface antigen (HBsAg) plus anti-hepatitis B core protein (HBc), and HBV DNA before chemotherapy. HBV DNA levels should be monitored monthly in all HBV-positive patients who do not receive prophylaxis. HBsAg-positive haematologic patients and those undergoing HSCT should receive third-generation antiviral therapy as prophylaxis. Anti-HBc-positive lymphoma patients and those receiving HSCT should receive antiviral prophylaxis. All HBV-negative haematologic patients should be vaccinated for HBV. The acquisition of data from well-designed studies is desirable in the near future. **L. Sarmati, Clin Microbiol Infect 2017;23:935**

Introduction

Hepatitis B virus (HBV) reactivation in haematologic patients has been associated with chemotherapy interruption, frequent hospitalization, progression to hepatic failure and death [1]. All of these conditions are largely preventable by the corrective measures of screening and prophylaxis. The grade of HBV reactivation risk for haematologic treatments and the length of immunosuppression are not always clearly quantifiable. Despite suggestions of experts from existing international guidelines, and given the lack of controlled studies, many areas remain unclear, primarily concerning which haematologic patients are at a higher risk of HBV reactivation and the type and duration of HBV reactivation monitoring, prophylaxis or preemptive therapy. These topics deserve further attention.

This document constitutes the recommendations of the Italian Society of Infectious Diseases (SIMIT), the Italian Society of Haematology (SIE), the Italian Group of Bone Marrow Transplantation (GITMO) and the Italian Society of Virology (SIVIM). Here we summarize the current evidence on HBV screening, monitoring, prophylaxis and therapy of HBV reactivation in patients with haematologic malignancies and/or patients who underwent haematologic stem cell transplantation (HSCT). Finally, it highlights the current gaps in knowledge on this topic.

Methods

This position paper was developed from one meeting held in Rome in July 2015 that involved a team of experts from the SIMIT, the SIE, the GITMO and the SIVIM. It is based on a systematic literature review [2]. The initial article underwent several rounds of review by authors. The results of our systematic review [2] were evaluated by Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (http://gdt.guidelinedevelopment.org/app/handbook/handbook.html) to provide a systematic method of grading both the strength of the recommendation (weak or strong) and the quality of evidence (very low, low, moderate and high). According to GRADE criteria, evidence from randomized controlled studies, initially considered of high quality, were rated down if there was risk of bias, inconsistency of results, indirectness of evidence, imprecision of results and publication bias. On the other hand, evidence from some observational studies, initially considered of low quality, were rated at high quality if there was a large magnitude of effect. Moreover, observational studies were considered to provide relevant information on the outcome of patients with haematologic malignancies.

HBV screening and monitoring: Who should be screened before chemotherapy? Which screening tests should be used? Should HBV-DNA detection be used to monitor HBV reactivation before starting antivirals? What is the best timeline to monitor HBV reactivation?

(*See systematic review, pages 3–5.*)

The purpose of HBV screening and monitoring is to identify haematologic patients with HBV infection who may benefit from receiving antiviral drugs (such as prophylaxis or preemptive therapy) and to check for possible reactivation of HBV replication.

Who should be screened before chemotherapy? Which screening tests should be used?

All patients with a diagnosis of haematologic malignancy and/or patients who should receive HSCT should be screened for HBV infection before beginning chemotherapy. Screening allows the early identification of patients with preexisting HBV infection (resolved or chronic) who may benefit from antiviral prophylaxis or preemptive antiviral treatment. There are no prospective, randomized studies on HBV screening in patients with haematologic malignancy to establish the advantages of one screening approach over another (hepatitis B surface antigen (HBsAg) plus anti–hepatitis B core protein (HBc), and HBV DNA in anti-HBc positive subjects), and therefore there is no agreement among international guidelines on which screening tests should be used [3–7].

We suggest that HBV screening should include serologic assays for HBsAg, anti-HBc and anti-HBs. Patients identified as HBsAg-positive/anti-HBc-positive or HBsAg-negative/anti-HBc-positive with or without anti-HBs-positivity should be tested for quantitative HBV DNA (***strong recommendation, moderate quality of evidence***).

Should HBV-DNA detection be used to monitor HBV reactivation before starting antivirals? What is the best timeline to monitor HBV reactivation?

All haematologic patients receiving chemotherapy and/or immunotherapy and patients who underwent HSCT with resolved or chronic HBV infection who have not received prophylaxis should be monitored monthly for HBV DNA detection (***strong recommendation, moderate quality of evidence***).

In patients with chronic HBV infection receiving antiviral prophylaxis, monitoring for reactivation should be performed before the end of prophylaxis, periodically thereafter and most likely also during the prophylaxis period (***strong recommendation, high quality of evidence***).

In patients with resolved HBV infection receiving antiviral prophylaxis, there are no data supporting HBV DNA monitoring for reactivation (***no recommendation, knowledge gap***).

Comments

An unresolved issue is the timing of HBV reactivation monitoring in patients with resolved HBV infection and chronic haematologic diseases (chronic lymphocytic leukaemia (CLL), chronic myeloid leukaemia (CML) and multiple myeloma (MM)) receiving chemotherapy (i.e. BCR-ABL tyrosine kinase inhibitors for CML) throughout their lifetimes. This condition might put them at risk of HBV reactivation for a long time, if not for life.

Prophylaxis in HBsAg-positive patients: Which antiviral drugs should be used to treat HBsAg-positive patients? How long should antiviral prophylaxis be provided to HBsAg-positive patients?

(*See systematic review, pages 5–6.*)

The incidence of HBV reactivation in HBsAg-positive haematologic patients who are not treated with antiviral therapy and who undergo chemotherapy is 10% to 50% and is associated with higher mortality rates [8–10].

Which antiviral drugs should be used to treat HBsAg-positive patients?

All HBsAg-positive patients, regardless HBV DNA levels, should receive anti-HBV drugs. The efficacy of lamivudine is hampered by the development of mutations in the tyrosine–methionine–aspartate–aspartate (YMDD) motif of the HBV polymerase gene, resulting in lamivudine resistance [11]. Furthermore, the most recent studies have reported incidences of HBV reactivation (breakthrough) ranging from 20% to 30% in HBsAg-positive lymphoma patients receiving prophylaxis with lamivudine (https://liverlearning.aasld.org/aasld/2014/thelivermeeting/61727/giuseppe.gentile.efficacy.and.safety.of.long.term.tenofovir.in.high.risk.html?f=p16m3l1147) [12–14].

The use of third-generation antiviral drugs (entecavir or tenofovir) is recommended in HBsAg-positive haematologic patients regardless of HBV DNA levels (***strong recommendation, moderate quality of evidence***).

Currently, entecavir and tenofovir, drugs with high genetic barriers to resistance, are preferred to lamivudine for the treatment of haematologic patients with chronic HBV infection regardless of their HBV DNA levels (entecavir: ***strong recommendation, high quality of evidence***; tenofovir; ***strong recommendation, moderate quality of evidence***)

Comments

Both entecavir and tenofovir have excellent safety profiles without myelosuppressive effects [15,16]. Renal function and previous lamivudine use can guide the choice of antiviral drug in HBsAg-positive haematologic patients. In the case of patients with severe renal impairment, entecavir may be a better treatment option than tenofovir because it has a low risk of inducing proximal tubular dysfunction and renal insufficiency [17]. However, tenofovir is preferred to entecavir if a patient has previously received lamivudine therapy because a certain rate of resistance is expected [18].

How long should antiviral prophylaxis be provided to HBsAg-positive patients?

Antiviral prophylaxis should be initiated at least 1 week before or in concomitance with starting chemotherapy. It should be continued for the duration of chemotherapy and should be administered for at least 12 to 24 months after chemotherapy withdrawal (***strong recommendation, moderate quality of evidence***).

Subsequent monitoring for delayed HBV reactivation after the cessation of antiviral prophylaxis is essential (***strong recommendation, high quality of evidence***).

Comments

The duration of antiviral treatment after chemotherapy interruption is the subject of debate because currently there are no randomized studies evaluating the optimal duration of post-chemotherapy treatment. In particular, whether entecavir and tenofovir should be administered for a defined time or indefinitely in patients with active hepatitis depends on the baseline HBV DNA levels (>4 $\log_{10}$ copies/mL), on aminotransferase levels and on the degree of fibrosis or cirrhosis [19]. The disappearance of HBV DNA and HBsAg associated with the appearance of anti-HBs are indicative of resolved infection and allow the suspension of antiviral therapy. For HBsAg-positive patients who undergo HSCT, there is a debate about how long to continue antiviral treatment because of the paucity of data on the optimal duration of therapy; however, it is clear that subsequent monitoring for delayed HBV reactivation after the cessation of antiviral prophylaxis is reasonable.

Prophylaxis in patients with resolved HBV infection: Which patients with resolved HBV infection should receive antiviral prophylaxis? Which antiviral drug should be used? How long should antiviral prophylaxis be provided?

(*See systematic review, pages 5–6.*)

HBV reactivation in patients with resolved hepatitis (HBsAg negative, anti-HBc positive, anti-HBsAg positive or negative) is an issue of growing relevance in the context of immunocompromised patients, particularly in the setting of haematologic malignancies. The incidence of HBV reactivation in this category of patients not receiving antiviral prophylaxis has been reported to be between 4.1% and 41.5% (Buti *et al.*, 'Tenofovir DF prevents HBV reactivation in anti-HBc positive patients with haematologic malignancies treated with rituximab: 12-months results of a randomized study (PREBLIN study),' Hepatology 2014;60(4 Suppl):997A, abstract 1661) [20–24].

Which patients with resolved HBV infection should receive antiviral prophylaxis? Which antiviral drug should be used? How long should antiviral prophylaxis be provided?

Patients with lymphoma and resolved HBV infection

In patients with lymphoma and resolved HBV infection, entecavir and tenofovir should be considered the drug of choice for HBV prophylaxis; lamivudine can be considered an alternative drug option (***weak recommendation, moderate quality of evidence***).

Comments. Two randomized studies in which first-line prophylaxis with entecavir and tenofovir was used to prevent HBV reactivation in patients with haematologic malignancy and resolved hepatitis have been conducted (Buti *et al.*, "Tenofovir DF prevents HBV reactivation …') [22]. No controlled studies that have been published on the use of lamivudine in the same category of patients.

Lamivudine is a safe and well-tolerated drug in immunocompromised patients with resolved hepatitis, even if its use must be carefully monitored for the possible emergence of resistant virus strains. However, the potential risk of lamivudine resistance development is small in patients with resolved HBV infection and undetectable HBV DNA, and in those who are expected to receive antiviral prophylaxis for less or more than 6 months. Therefore, although economic studies (costs and resource use) were not identified on this topic, given that lamivudine has the lowest cost, it is reasonable choose the least expensive antiviral drug in this setting.

Antiviral prophylaxis should be initiated at least 1 week before or in concomitance with starting chemotherapy and should be administered at least for 12 months after chemotherapy interruption (***strong recommendation, moderate quality of evidence***).

Comments. Although there is agreement on the optimal start time of prophylaxis in the weeks before beginning chemotherapy, little is known about the best time to discontinue HBV prophylaxis. The period of immune recovery is probably the best time to stop antiviral prophylaxis; however, the lack of reliable biologic markers of immune recovery prevents the definition of the optimal duration of prophylaxis, particularly in patients with haematologic malignancies. The incidence of delayed HBV reactivation after the cessation of antiviral prophylaxis in lymphoma patients with resolved HBV infection is unknown.

Patients with acute T cell leukaemia (ATL), MM, CLL and other haematologic malignancies with resolved HBV infection

Haematologic patients with ATL, MM and CLL with resolved HBV infection should receive antiviral prophylaxis (***weak recommendation, low quality of evidence***).

Lamivudine should be the drug administered in patients with CLL for 12 months' therapy (***weak recommendation, low quality of evidence***), while there are no studies on HBV antiviral prophylaxis in ATL and MM patients (***no recommendation, knowledge gap***).

Comments. Three cases of HBV reactivation in HBsAg-positive CML patients and one case in a CML patient with resolved HBV infection during BCR-ABL tyrosine kinase inhibitor (i.e. imatinib, dasatinib) treatment have been described in the literature [25–28]. Currently, there are no studies describing a better intervention strategy to monitor or prevent HBV reactivation in CML patients during tyrosine kinase inhibitor therapy. Regarding CLL, caution in the administration of ibrutinib and idelalisib is suggested in HBV-positive patients, but the best intervention strategy is not yet known (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003843/WC500175377.pdf) [29].

HBV infection management strategy in autologous (auto-HSCT) and allogeneic HSCT (allo-HSCT): Which HSCT recipients should receive antiviral prophylaxis? Which antiviral drug should be used? How long should antiviral prophylaxis be provided?

(*See systematic review, page 6 and Supplementary Appendix 3 and 4.*)

HSCT, and in particular allogeneic HSCT (allo-HSCT), is a condition associated with a high risk for HBV reactivation, with a lower rate reported in patients with resolved infection and a higher rate reported in HBsAg-positive recipients.

Which HSCT recipients should receive antiviral prophylaxis? Which antiviral drug should be used? How long should antiviral prophylaxis be provided?

HBsAg-positive auto- and allo-HSCT recipients

All HBsAg-positive HSCT recipients should be treated independent of the presence or the level of HBV DNA (***strong recommendation, moderate quality of evidence***).

Antiviral treatment should be conducted with entecavir or lamivudine (***strong recommendation, moderate quality of evidence***)

Antiviral drugs should be started at least a week before the HSCT procedure and should be continued for at least 1 year (***strong recommendation, moderate quality of evidence***).

Comments. In HBsAg-positive patients undergoing HSCT, the only high-genetic-barrier antiviral drug used was entecavir; no data are available on tenofovir use in this kind of patient. Regarding the duration of antiviral treatment, given the high overall mortality of HSCT patients, limited information is present in the published studies. However, it is reasonable to consider lifelong antiviral treatment in these patients. The disappearance of HBV DNA and HBsAg associated with the appearance of anti-HBs are indicative of resolved infection and allow antiviral therapy to be suspended.

Auto- and allo-HSCT recipients with resolved HBV infection

All anti-HBc-positive HSCT recipients should receive prophylaxis with lamivudine, independent of the presence of HBV DNA, for a time period of at least 18 months (***strong recommendation, moderate quality of evidence***).

Comments. Ideally, the duration of antiviral prophylaxis should be based on immune recovery (i.e. increased $CD4^+$ counts above 200–400 cells/cubic millimeter), which can take years after allo-HSCT. Close monitoring of viraemic rebound and seroreversion should be performed when prophylaxis is discontinued. The timing of monitoring is not actually defined.

HBV-negative allo-HSCT recipient with an anti-HBV-positive donor

All HBV-negative allo-HSCT recipients with anti-HBc-positive/anti-HBs-positive or -negative (HBV DNA negative) donors should receive prophylaxis with lamivudine (***weak recommendation, moderate quality of evidence***). The lamivudine prophylaxis duration is not defined (***no recommendation, knowledge gap***).

Choice of antiviral drugs for the treatment of HBV reactivation: Should third-generation anti-HBV drugs be preferred to first- or second-generation antiviral drugs in the treatment of HBV reactivation with or without hepatitis flare in haematologic patients?

There are no studies which directly compare the clinical efficacy of third-generation antiviral drugs vs. first- or second-generation anti-HBV drugs in the treatment of HBV reactivation, with or without hepatitis, during immunosuppressive chemotherapy in haematologic patients. However, the severe consequences of this condition in these patients (chemotherapy interruption, frequent hospitalization, progression to hepatic failure and death) make the antiviral treatment of HBV reactivation indispensable. Therefore, the use of antiviral drugs with high potency and high barrier to resistance (third-generation anti-HBV drugs) is recommended (***strong recommendation, knowledge gap***).

Comments. In immunocompetent patients with chronic HBV infection, randomized studies demonstrated that the use of

entecavir vs. lamivudine, entecavir vs. adefovir or tenofovir vs. adefovir was associated with a higher rate of nondetectable HBV DNA [30–34]. In addition, in a network meta-analysis [35], the use of tenofovir showed a higher efficacy compared to lamivudine in inducing undetectable HBV DNA levels in the treatment of immunocompetent patients with chronic HBV infection.

The duration of antiviral therapy in the immunocompromised patient is expected to be prolonged (more than 12 months) as a result of the severity of HBV hepatitis manifestations and the need to continue immunosuppressive therapy. Reactivation of HBV in this kind of patients is usually related to high levels and prolonged virus replication despite use of antiviral drugs, thus promoting the selection of resistant strains during treatment with low-genetic-barrier antiviral drugs, such as lamivudine. Entecavir and tenofovir have greater antiviral potency compared to lamivudine, and their use is associated with low or no selection of drug-resistance mutations [36,37]. Recently tenofovir alafenamide, a novel targeted prodrug of tenofovir, was tested in two randomized studies in treatment-naive immunocompetent subjects with chronic HBV infection. It was shown to be noninferior and associated with less bone and renal adverse effects than tenofovir [38,39].

Only a retrospective study [40] and two case series [41,42] described successful treatment with drugs with higher antiviral potency and high genetic barrier, such as entecavir or tenofovir, in haematologic patients.

Immunization against HBV in patients with haematologic malignancies and/or patients who underwent HSCT: Should these patients be vaccinated? Which HBV vaccination schedule should be adopted?

(*See systematic review, page 6.*)

All patients with haematologic malignancies and/or patients undergoing HSCT who are HBV negative at screening should undergo HBV vaccination, and their anti-HBs titre should be periodically monitored (***strong recommendation, low quality of evidence***).

A standard vaccination schedule (20 μg at 0, 4 and 6 months) is generally recommended; however, an intensive schedule with four single 20 μg HBV vaccine doses administered at 0, 2, 4 and 6 months may be an alternative to the conventional protocol, with the ultimate aim of obtaining a better vaccination response (***strong recommendation, low quality of evidence***).

Comments. In general, in adults with haematologic malignancies, including acute leukaemia and other myeloproliferative diseases, an anti-HBV vaccine should be administered 1 to 2 weeks before the initiation of or 3 months after completion of chemotherapy [43].

HBV vaccination of HBV-negative auto- or allo-HSCT patients should be performed before beginning the conditioning regimen. In the allo-HSCT setting, vaccination of donors for HBV-positive recipients is also suggested, with the goal that the adaptive immune response from the HBV-vaccinated donor could protect the recipient from HBV reactivation [44].

Conclusions

The majority of the questions on HBV screening and monitoring, on HBV prophylaxis in patients with chronic or resolved HBV infection and on the management of HBV infection in HSCT were addressed by recommendations with a moderate quality of evidence. HBV immunization and treatment of HBV reactivation were supported by studies with low quality of evidence. Knowledge gaps remain regarding HBV reactivation monitoring in patients with resolved infection receiving lamivudine and on the duration of prophylaxis in HSCT recipients from an HBV-positive donor. Moreover, to date, the scientific literature does not provide guidance (i.e. knowledge gap) in ATL and MM patients with resolved HBV infection.

There is a great need in the near future of high-quality studies, mainly randomized controlled trials, that provide clear indications on the following: the risk of HBV reactivation in haematologic diseases other than lymphoma; the risk of HBV reactivation as a consequence of new target biologic treatment use; the duration of HBV prophylaxis in either HBsAg-positive or anti-HBc-positive haematologic patients receiving chemotherapy immunotherapy or HSCT; the duration of HBV DNA monitoring after withdrawal of antiviral therapy; the best drug or combination of drugs for HBV hepatitis flare therapy; and the most protective HBV immunization schedule in haematologic patients.

Acknowledgements

The authors represent the following Italian societies: SIE (FP, MP), GITMO (WA, CG, AR), SIVIM (GA, VS) and SIMIT (MA, RB, NC, GBG, MG, GG, MM, CFP, MP, GT, LS).

Transparency declaration

SL: Gilead Fellowship Programme 2015, received travel grants from Gilead Sciences, Merck Sharp & Dohme and Bristol-Myers Squibb; payment for lectures from Merck Sharp & Dohme, Gilead Sciences, Bristol-Myers Squibb and Abbvie; and research funding from Gilead Sciences. AG received grants/research support from bioMérieux, ELITechGroup, EMD Serono, Siemens Healthineers and ViiV Healthcare. GG: Gilead Fellowship Programme 2015, received travel grants from Gilead Sciences; payment for lectures from Pfizer and Gilead Sciences; and research funding from Gilead Sciences. AM received speaker fees, travel grants, and consulting fees from Abbvie, Bristol-Myers Squibb, Gilead Sciences, Merck Sharp & Dohme, ViiV Healthcare and Janssen-Cilag. PM received grants/research support from ViiV Healthcare and Gilead Sciences; honoraria or consultation fees from ViiV Healthcare, Gilead Sciences, Abbvie, Merck Sharp & Dohme, Bristol-Myers Squibb, Roche and Beckman Coulter; and travel grants from ViiV Healthcare, Gilead Sciences and Abbvie. GGB received speaker fees from Abbvie, Bristol-Myers Squibb, Gilead Sciences, Merck Sharp & Dohme, Janssen-Cilag and BioTest. PCF is a consultant for and received grants from ViiV Healthcare, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck Sharp & Dohme, Roche and AbbVie. SV: Gilead Fellowship Programme 2015, received grants from Bristol-Myers Squibb (424-1007), Gilead Sciences and Roche. CN received personal fees from AbbVie, Gilead Sciences and Bristol-Myers Squibb. BR received speaker and consultations fee from Abbvie, Bristol-Myers Squibb, Gilead Sciences and Merck Sharp & Dohme. All the other authors report no conflicts of interest relevant to this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.cmi.2017.06.023.

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