Scientific Review of the Knowledge Gap in the Efficacy of Antiviral Therapy to a Low-Risk Kidney Transplant Population Cohort

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Abstract

Opportunistic infection with cytomegalovirus (CMV) is a major cause of patient morbidity and mortality after renal and other solid organ transplantation [1]. De facto standard of care is choice of either prophylactic or preemptive therapy [2]. There is a knowledge gap in the efficacy of antiviral therapy to a low-risk kidney transplant population. I searched the PubMed and clinicaltrials.gov databases with strategic keywords. Although the final search yielded 52 results (PubMed) and 25 (clinicaltrials.gov), I only included 14 articles particular to the main topic of this review. There is limited data specific to this population, therefore, healthcare defaults to the de facto standard of care of choice.

Introduction

End Stage Renal Disease is an end organ diagnosis where the kidneys lose optimal functioning. Two treatment options for this disease are dialysis or kidney transplantation. Dialysis is a process of removing or filtering waste, via a machine, from the blood. Although it is effective, it is not without harmful side effects. The latest studies reveal a significant decrease in mortality with kidney transplant compared to dialysis. This is a reason why most providers encourage their patients to pursue kidney transplantation. Once a patient is transplanted, there is an expected recovery phase. Typically, the first 3 months post-operation is a high-risk period. The patient would have endured significant immunosuppression therapy, which puts the patient at risk for opportunistic infections (viral, bacterial, and/or fungal). This is the reason why antivirals, antibiotics, and antifungals are a staple regimen alongside immunotherapy.

This systematic review will focus on the antiviral regimen. Antivirals are for protection from viruses such as herpes and cytomegalovirus. Cytomegalovirus (CMV) is a major infection that can be very harmful to the donor kidney organ. CMV is a pervasive post-transplant infection, which is how it earned the nickname, the transplantation troll (Kotton, 2018). A post-transplant patient could get infected from a CMV seropositive organ or from the community. Latest research showed that 20%-60% of kidney transplant recipients developed CMV within first 3 months post-transplant [3]. Various post-transplant CMV risk factors include serostatus, rejection history, host factors, and net state of immunosuppression [4]. CMV infections typically lead to febrile illness, opportunistic infections, acute graft rejection and potentially graft failure [1]. The antiviral medication of choice is high dose valacyclovir and research has explored various treatment regimen strategies, prophylaxis vs preemptive or a hybrid of both (Kotton, 2018).

In the transplant community, universal prophylaxis has been accepted as the standard. Universal prophylaxis is treating all post-transplant patients, within 10 days post operation, and continuing for 3-6 months [4]. Transplant recipients that are CMV
seronegative and receive donor CMV seropositive organs (D+/R-)
are considered high risk for CMV. The guidelines uniformly
suggest six months of valganciclovir prophylaxis [4]. Transplant
recipients that are CMV seropositive (R+), regardless of donor
serostatus, are considered intermediate risk and recommended to
receive three months of valganciclovir prophylaxis [4]. Prophylaxis
disadvantages are drug toxicity, cost, antiviral resistance, delayed
T cell response recovery, and late onset CMV. Preemption
therapy (PET) takes a reactive approach to immunotherapy. The
regimen consists of serial blood tests, symptoms monitoring, then
medication treatment only if symptoms meet infection criteria
[3]. However, PET doesn’t protect against herpes simplex and is
logistically difficult to coordinate and monitor (Kotton, 2018).
Numerous research studies concentrate on comparing the two
therapy philosophies to discover the superior therapy. On the other
hand, this review will focus on the efficacy of using antivirals for
low-risk kidney transplant population, defined as CMV negative,
hepatitis C virus (HCV) negative, and Epstein Barr virus (EBV)
negative. These patients are designated as donor seronegative/
recipient seronegative (D-/R-).

Background

It is understood that post-transplant patients need protection
from CMV. D+/R- patients are considered high risk for CMV as
it occurs in 70% of these cases [5]. However, for patients that are
not exposed to CMV, and receive an organ that isn’t exposed to
CMV, there begs the question if antiviral therapy is indicated. In
reviewing the latest studies, there is limited data on the efficacy
of using antivirals for the low-risk kidney transplant population
(D-/R-). One thing to consider is the increased risk for side effects.

Another consideration is the increased risk for CMV or other viral
resistance. Antiviral, though effective options, can be limited in
their effectiveness and adequateness. Acyclovir, though safe and
inexpensive, is inferior to cytomegalovirus replication. Ganciclovir,
another compelling option, is also susceptible to antiviral resistance
[6]. Valganciclovir is costly and with significant side effects [4].

In reference to the preemption vs prophylaxis discussion, CMV
DNAemia is more common with preemptive therapy, whereas
late-onset CMV DNAemia or disease and neutropenia is more
common with prophylaxis (Kotton, 2018).

Methods

In PubMed, I used search terms “cytomegalovirus antiviral
prophylaxis transplant” (Table 1). The search yielded 2269 results.
I was able to find some articles that pertained to my research
questions, but I noticed the extensive dating. I adjusted the date
filter to “2010-2022” and retrieved 1043 results. As I reviewed
articles, I noticed I didn’t have access to many articles of interest.
I adjusted the search filter to only include “free full text” articles.
The results yielded 424 articles. I chose a few articles that
specifically reviewed cytomegalovirus, as an antiviral treatment
for post-transplant recipients. I excluded articles that didn’t pertain
to kidney or liver transplant because they share the same standard
antiviral regimen. I excluded articles that reviewed antivirals other
than valganciclovir because this is standard antiviral medication.

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than valganciclovir because this is standard antiviral medication.

The articles ranged from the American Journal of Transplantation,
Current Opinion in Infectious Diseases, the Transplantation
Journal, Current Hematologic Malignancy Reports. I specifically
sought articles that focused on or at least mentioned CMV
seronegative donors and recipients.

Table 1: Initial Search Terms.

<table>
<thead>
<tr>
<th>Search Terms</th>
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Although I came across articles that helped me frame the research introduction and background, most of the articles focused on CMV seropositive donors and seronegative recipients. Therefore, I did an additional PubMed search with terms “antiviral seronegative donor seronegative recipient transplant” (Table 2). Also, I included “free full text” and “2015-2022” as filters. My updated search yielded 52 results. To find more information specific to the D-/R- cohort, I searched the clinicaltrials.gov database for latest data. I used key terms “CMV prophylaxis, kidney transplant” which yielded 44 results (Table 2). I applied an additional filter for completed studies, which reduced my results to 25. I excluded pediatric studies and drug intervention comparison studies. Although it was difficult to find studies specific to the D-/R- cohort, I was able to locate information on pipeline therapies to address CMV infection. The HB-101 vaccine recently completed Phase II and it included the D-/R- cohort as a control (National Library of Medicine [NLM], NCT03629080). What is interesting is that this article did not identify the D-/R- cohort as a high-risk population. Hoffmann-La Roche completed a study that looked at the effects of Ganciclovir on cohort, D+/R- and an untreated cohort D-/R- (National Library of Medicine [NLM], NCT01663740). The findings were either comparable or the D-/R- cohort showed superior findings. This isn’t surprising as they are a low-risk cohort. Figure 1 illustrates a flow chart that illustrates the search methodology.

Table 2: Second set of Search Terms.

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Figure 1: Flowchart of search methodology.
The following table includes the evaluation of resources included.

<table>
<thead>
<tr>
<th>Title/Author with Full Citation</th>
<th>Study Aims and or Hypothesis</th>
<th>Study Design</th>
<th>Study Population</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Legrande, C. M., New- man, D. J., Keating, M. R., Maclean, G. D., &amp; Grant, D. M. (2000).</td>
<td>A cost-effectiveness analysis of treatment with valaciclovir versus placebo was performed, assessing the mean total cost for the number of cases of CMV avoided at 6 months in the two groups</td>
<td>multicenter multinational randomized, placebo-controlled, double-blinded trial of valaciclovir CMV prophylaxis. Patients were stratified into donor seropositive/recipient seronegative (D+/R-) and recipient seropositive (R+) groups. Patients were followed up 6 months posttransplant for clinical efficacy and 1 year for patient/allograft survival</td>
<td>15 to late 70’s Even Male/Female ratio</td>
<td>*CMV disease incidence at 6 months posttransplant were 16% for the valaciclovir group and 45% for placebo controls in the D+/R- stratum and 1 and 6% for the valaciclovir group and placebo controls</td>
</tr>
<tr>
<td>Couchoud, C., Cachurat, M., Haugh, M., Poulet-Noble, C.</td>
<td>The aim of this meta-analysis was to assess the efficacy of antiviral agents to prevent, in solid organ transplant recipients, CMV infection and symptomatic disease and to decrease the incidence of acute rejection, graft loss, and death</td>
<td>prospective randomized study, where one group in the study received a prophylactic treatment with acyclovir and/or ganciclovir (GCV) or valaciclovir prophylaxis as most cost effective when compared to preemptive IV ganciclovir and standard therapy</td>
<td>adults or pediatric recipients of a solid organ transplant</td>
<td>Significant decrease in CMV infection, however, no decrease in graft loss, acute rejection, or death</td>
</tr>
<tr>
<td>Puisis, Y. A. &amp; Smythman, D. R. (2007).</td>
<td>Reviewing the risks and benefits of differing strategies</td>
<td>Metanalysis of randomized controlled trials</td>
<td>D+/R- CMV recipients</td>
<td>*Hodson et al metaanalysis, prophylaxis-CMV risk reduced by 60%, mortality reduced by 40% and preemptive therapy was ineffective</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Boillat Blanco, N., Pascual, M., Venetz, J., Nseir, G., Meylan, P., Manuel, O.</th>
<th>Impact of a Preemptive Strategy After 3 Months of Valganciclovir Cytomegalovirus Prophylaxis in Kidney Transplant Recipients. Transplantation: January 27, 2011. Volume 91(2), p 251-255 doi: 10.1097/TP.0b013e318200b9d0</th>
<th>Assess impact of preemptive strategy, after discontinuing antiviral prophylaxis, in prevention of late onset CMV; primary endpoint was incidence of late-onset CMV</th>
<th>Prospective, non-controlled, single center</th>
<th>86 kidney transplant recipients, average age 48 years, 60 Male 26 Female 30 D+/R- 56 R+</th>
<th>*CMV occurred in 36% recipients; 43% in D+/R- 32% in R+</th>
<th>*None from the R+ group developed late onset CMV, and their PCR results were below threshold</th>
<th>*Preemption strategy seems to have a limited impact on the prevention of late-onset CMV disease, particularly in group of seropositive CMV patients</th>
</tr>
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<tbody>
<tr>
<td>van der Beek, M., Berger, S., Vossen, A., van der Blij-de Brouwer, C., Press, R., de Fijter, J., Claas, E., Kroes, A., loys, C.</td>
<td>Preemptive Versus Sequential Prophylactic-Preemptive Treatment Regimens for Cytomegalovirus in Renal Transplantation: Comparison of Treatment Failure and Antiviral Resistance. Transplantation: February 15, 2010 - Volume 89 - Issue 3 - p 320-326 doi: 10.1097/TP.0b013e318181be0301</td>
<td>Compare the incidence and course of CMV infections, frequency of treatment failure of CMV infections, and role of antiviral resistance</td>
<td>*Retrospective Single center</td>
<td>*78 D+/R- kidney-pancreas transplant recipients</td>
<td>*Incidence of CMV was similar for both cohorts</td>
<td>*Preemption cohort had significantly higher CMV 69% vs 45%</td>
<td>*No CMV end organ disease occurred in any cohort</td>
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<td></td>
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<td>*42 treated preemptive and 29 treated prophylactic</td>
<td>*Mean age Prophylaxis 49; Preemption 46</td>
<td>*No significant difference in # of rejection episodes or renal function between the cohorts</td>
<td>*Treatment failure, defined by DNA load, was higher in preemtion group 71% vs 14% &amp; duration of preemtion treatment was longer with preemption cohort 45 days vs 29 days</td>
<td>*Sequential prophylaxis-preemptive approach proved practical</td>
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<td>*Prior to 2006, preemptive regimen started, guided by CMV DNA load.</td>
<td>*Males Prophylaxis n24; Preemption n18</td>
<td>*CMV infections with a slow response to preemptive antiviral treatment occurred less frequently in patients who had received prophylactic treatment than in patients on a strictly preemptive regimen.</td>
<td>*CMV infections with resistant virus were eventually cleared without switching antiviral therapy</td>
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Define particularly high-risk groups

<table>
<thead>
<tr>
<th><em>Prospective, single center</em></th>
<th><em>Cohorts with differing immunosuppressive regimens</em></th>
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<tr>
<td><em>n94 renal transplant recipients</em></td>
<td><em>Age &gt;18 years</em></td>
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This review will discuss recent developments in CMV antiviral agents and non-pharmacologic interventions that may augment the ability to prevent and treat CMV infections in recipients

<table>
<thead>
<tr>
<th><em>Adaptive therapy entails recombination of CMV specific T cells by translation of donor T cells</em></th>
<th><em>IVIG not effective in CMV therapy</em></th>
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<tbody>
<tr>
<td><em>Monoclonal antibody therapy still in development</em></td>
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</table>


*Our study compares outcomes and costs of adult renal transplant recipients randomized to receive prophylactic or preemptive oral ganciclovir for the clinical management of CMV infection*

*The primary outcome for the purpose of powering the study was an economic comparison between the prophylactic and preemptive groups. Secondary outcomes included occurrence of CMV infection and disease, clearance of CMV DNAemia, incidence of acute rejection, allograft survival, allograft dysfunction, death, and incidence of neutropenia.*


*Randomized single center*  
*Prophylaxis cohort (n50), preemptive cohort (n49) with VGCV, 1:1 block design stratified by CMV serostatus*

*Monitored by PCR before transplant then weekly for 16 sela post-transplant, then at months 5, 9, 12*  
*Prophylaxis group received VGCV for 100 days post-transplant while preemptive only received if PCR detected*  
*Prophylaxis group (age 52 years, male 51%, white 80%) Preemption group (age 49, male 23%, white 90%)*


*CMV risk population D+/R*, D*/R+, D-/R* were included, but only to monitor (control)  
*144 adult patients*  
*No deaths occurred*

*99% overall allograft survival rate*  
*Rejection (proph n1, preemp n6)*  
*No relationship observed between CMV and acute rejection*  
*No difference in serum creatinine between cohorts*  
*Preemptive reduction of CMV by 90% during first 100 days and by 52% for entire study compared to prophylaxis*

*In preemptive cohort, CMV onset occurred only in first 100 days (avg by 39 days post txp)*  
*Recurrent CMV higher in preemptive cohort (n14 vs n4)*

*This randomized study found that prophylaxis or preemptive treatment with ganciclovir was each associated with low rates of symptomatic CMV (5%) in kidney transplant recipients*

*No evidence of CMV recurrence*  
*Symptoms in CMV-proph group (n4) after 100 days treatment; preempt (n1) by 61 days post-transplant*  
*D*/R- cohort only had n2 (10%) with CMV DNAemia*

*Costs were favorable to prophylaxis (VGCV, hospitalization) but favorable to proph (provider time, CMV PCR testing)*  
*Preemption results suggest correlation with low risk of CMV occurrence in D*/R- group*

*3 suggested therapies based on results: (1) preemptive, since in this study the overall incidence of CMV DNAemia was similar, but symptomatic CMV was less than with prophylaxis; (2) extended prophylaxis to 6–12 months (26, 27) or (3) prophylaxis to approximate 100 days followed by monitoring and preemptive therapy.*

*Prophylaxis more effective in reducing CMV occurrence, however less effective in preventing symptomatic disease in D*/R- patients*  
*Costs were favorable to prophy (proph n1, preemp n4)*  
*99% overall allograft survival rate*  
*No deaths occurred*  
*Monoclonal antibody therapy still in development*
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Outcomes</th>
<th>Observations</th>
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<tr>
<td></td>
<td>*Viremia in D-/R- and R+ cohort who received lymphocyte-depleting induction therapy.</td>
<td>*Primary outcome was incidence of CMV viremia within first year post transplant.</td>
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<td>*Secondary outcome includes CMV syndrome incidence (fevers, myalgias, fatigue etc.), biopsy proven CMV, leukopenia or neutropenia, CMV related hospitalization, and biopsy-proven rejection</td>
<td>*Results that there is no increased risk of rejection or disease despite a shorter duration of VGCV use</td>
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|                                           | *No significant difference in CMV viremia in R+ groups | *No significant difference of CMV syndrome between the groups |
|                                           | *No significant difference in cohorts which validates 3 mos CMV prophylaxis as an effective strategy | *Results that there is no increased risk of rejection or disease despite a shorter duration of VGCV use |
|                                           | *Regarding D-/R-, there is minimal risk of CMV infection, and routine prevention of CMV is not necessary | *No correlation that aggressive VGCV prophylaxis strategy reduces the incidence of CMV viremia in D-/R- or R+ cohort who received lymphocyte-depleting induction |

|                                           | *Observational prospective | *Randomized parallel |
|                                           | *120 participants | *Age 14-75 years |
|                                           | *Seronegative patients receive 90-day GCV prophylaxis | *Seropositive patients undergo surveillance for early viremia detection |

*No correlation that aggressive VGCV prophylaxis strategy reduces the incidence of CMV viremia in D-/R- or R+ cohort who received lymphocyte-depleting induction

*First in-human Phase I trial to assess the safety and immunogenicity of 3 administrations of the candidate vaccine at ascending doses in healthy seronegative adult volunteers.


*Phase II
*Randomized double-blind Interventional parallel


*To compare spermatogenesis in male adult renal transplant recipients receiving valganciclovir versus untreated matched controls

*To compare spermatogenesis in male adult renal transplant recipients receiving valganciclovir versus untreated matched controls

*Randomized multicenter prospective interventional study

Table 3: Table of Included Studies.
<table>
<thead>
<tr>
<th>Title/Author with Full Citation</th>
<th>Strengths and Limitation of Study</th>
<th>Other Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Couchoud, C., Cucherat, M., Haugh, M., Pouteil-Noble, C. Cytomegalovirus Prophylaxis with Antiviral Agents in Solid Organ Transplantation: A Meta-Analysis. Transplantation: March 15, 1998 - Volume 65 - Issue 5 - p 641-647</td>
<td>Because not all the authors performed routine viral monitoring, the exact incidence of cytomegalovirus infection could not be assessed for all trials.</td>
<td>To date, there is no evidence to suggest that cytomegalovirus prophylaxis should be prescribed to reduce the incidence of acute or chronic rejection</td>
</tr>
<tr>
<td>Puius, Y. A. &amp; Snydman, D. R. (2007). Prophylaxis and treatment of cytomegalovirus disease in recipients of solid organ transplants: current approach and future challenges. Current Opinion in Infectious Diseases, 20 (4), 419-424. doi: 10.1097/QCO.0b013e32821f6026.</td>
<td>*Randomized control study *No clear effect on acute rejection *Sparse data for preemptive therapy *No data on seronegative donor and seronegative recipient</td>
<td>*Strippoli et al. meta analysis, 17.8% patients (64/358) excluded because of early CMV onset (days 0-10) *Endpoints of rejection and mortality not addressed *Prophylaxis relies on costly drugs *Preemption relies on costly testing for CMV monitoring *And the treatments for CMV &amp; rejection are costly *Resistance can occur in the absence of prophylaxis</td>
</tr>
<tr>
<td>Boillat Blanco, N., Pascual, M., Venetz, J., Nseir, G., Meylan, P., Manuel, O. Impact of a Preemptive Strategy After 3 Months of Valganciclovir Cytomegalovirus Prophylaxis in Kidney Transplant Recipients. Transplantation: January 27, 2011. Volume 91(2),p 251-255 doi: 10.1097/TP.0b013e318218b9f0</td>
<td>*Data from first period of study collected retrospectively *No control group *Small cohort sample</td>
<td>D-/R- patients were excluded</td>
</tr>
<tr>
<td>van der Beek, M., Berger, S., Vossen, A., van der Blij-de Brouwer, C., Press, R., de Fijter, J., Claas, E., Kroes, A., joys, C. Preemptive Versus Sequential Prophylactic-Preemptive Treatment Regimens for Cytomegalovirus in Renal Transplantation: Comparison of Treatment Failure and Antiviral Resistance. Transplantation: February 15, 2010 - Volume 89 - Issue 3 - p 320-326 doi: 10.1097/TP.0b013e318181bc0301</td>
<td>The cost effectiveness of both regimens is a relevant aspect in decision making. Costs may vary locally but depend among other things on the number of samples for CMV DNA load measurement, the amount of antiviral medication administered, and the number of admissions for CMV infections.</td>
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</table>
*D-/R- & preemption cohorts received acyclovir x100 days post-transplant for herpes prophylaxis  
*No significant side effects of oral VGCV  
*No clinical or viral evidence of resistance  
*Costs evaluation suggests the transplant center may need to absorb the PCR testing and that MCR part D significantly covers VGCV |
*CMV defined as unexplained fever (greater than 38.0 for 3+consecutive days and positive blood or urine sample  
*Allograft rejection defined as elevation in serum creatinine of at least 0.4mg/dl, usually with reduced urine output and renal biopsy |


Table 4: Study Evaluation Table.

Results

The results of the integrative review indicate, for cytomegalovirus prophylaxis, there is no common opinion concerning its necessity and efficacy [6]. A search specific to the D-/R- cohort was lacking. Instead, there were far more articles investigating treatment strategies, prophylaxis vs preemption. Though, no strategy proved significantly dominant over the other. Preemption is less costly than prophylaxis, but it requires frequent monitoring and still carries risks of rejection, dysfunction, and infections [7]. Meta-analyses & pooled analyses found no difference in mortality, graft loss, and acute rejection, between prophylaxis vs preemption and none were identified as an independent risk factor of graft loss (Kotton, 2018).

Discussion

The trend in research is primarily focused on high-risk patients, and low risk patients have been insistently lumped into the consensus. It would be beneficial to the patient to avoid unnecessary medications, to minimize the identified risks. That is not to say that other infection risks should not be considered. Antiviral prophylaxis against other herpes infections (especially disseminated varicella and herpes simplex) with acyclovir, famciclovir, or valacyclovir should be considered (Kotton, 2018). It goes without saying that there should be ongoing efforts to investigate the correlation between cell-mediated immunity against CMV and high risk CMV infection [3]. One study estimated that monitoring CMV plasma viral load would have avoided approx. 1/3 of late onset CMV cases, however there are no subsequent
studies that evaluate this in routine clinical practice [8-10,3]. At this point, we can deduce that CMV prevention is not warranted for a low risk CMV seronegative donor/recipient cohort.

Conclusion

All in all, this review makes the case for further exploration into how to achieve this goal. A study can conduct a cost utility analysis to compare QALYs between the generally medicated vs the preemptive prophylactic approach. A cost of illness analysis can compare indirect/direct costs. Another option is a cost benefit analysis to investigate the difference in net benefits between both approaches.

Acknowledgement

I thank Dr. Parul Patel (Sutter Health Department of Transplantation) for his expertise and assistance throughout all aspects of writing this manuscript.

References


