Metro North Hospital and Health Service *Putting people first*

Research Workshop via Teams

Publishing Your Research: What to Report and How to Discuss Results

11 August 2020 – Teams Live

Facilitated by Prof Janet Davies
MNHHS Office of Research
MNHHS-Research@health.qld.gov.au

Queensland Government

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QUT

Agenda

Part 1 Publishing your research (20 min)

- Introduction: How to Discuss the Results

Part 2 Exemplary Primary Research Articles (10 min each)

Assoc Prof Steven Lane

Jak2V617F and Dnmt3a loss cooperate to induce myelofibrosis through activated enhancer-driven inflammation

Prof Jason Roberts

The Effect of Renal Replacement Therapy and Antibiotic Dose on Antibiotic Concentrations in Critically Ill Patients: Data From the Multinational Sampling Antibiotics in Renal Replacement Therapy Study

Part 3 Panel discussion and questions (15 min)

Please do not mention any confidential details of patients or research.

Microsoft Teams meeting

Facilitated by Professor Janet Davies
MNHHS Office of Research
MNHHS-Research@health.qld.gov.au

Professor Janet Davies

Assistant Director Research
Metro North Hospital and Health Service
Head, Allergy Research Group, QUT

- Multidisciplinary allergy research
- Current support: NHMRC, three ARC, NFMRI, other grants and industry engagements
- Author of over 80 research articles, 15 government reports, and 4 global positional papers, H index 23

Associate Professor Steven Lane

Clinical haematologist and Director Clinical Research in Cancer Care RBWH

Head, Cancer Program, and Gordon and Jessie Gilmour Leukaemia Research Lab, QIMR Berghofer

- Focused on molecular drivers and targeted cancer therapies.
- Supported by NHMRC Investigator Grant, CSL Centenary Fellowship, NHMRC project grants.
- Author of over 80 publications and H index of 29

Professor Jason Roberts,

Clinical Pharmacist RBWH

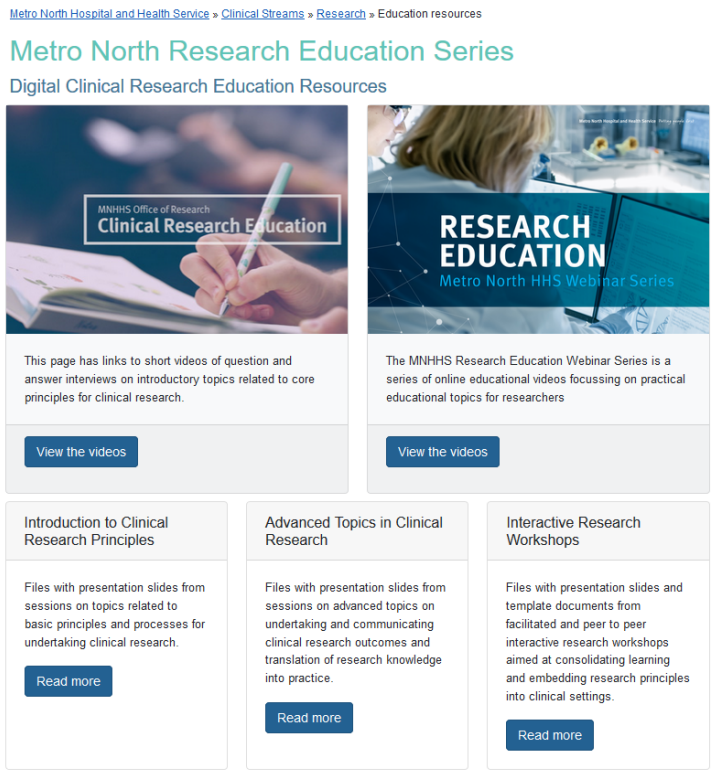
NHMRC Practitioner Fellow, UQ

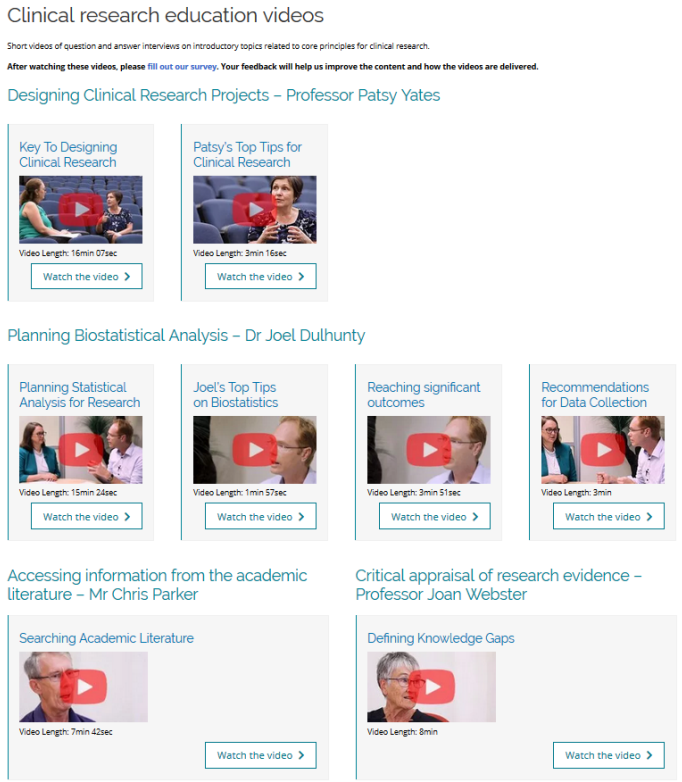
- Focused on communicable disease and critical care
- Director, NHMRC CRE REDUCE: to optimise antibiotic dosing regimens and slow antibiotic-resistant superbug emergence
- Author of over 400 publications and H index of 59

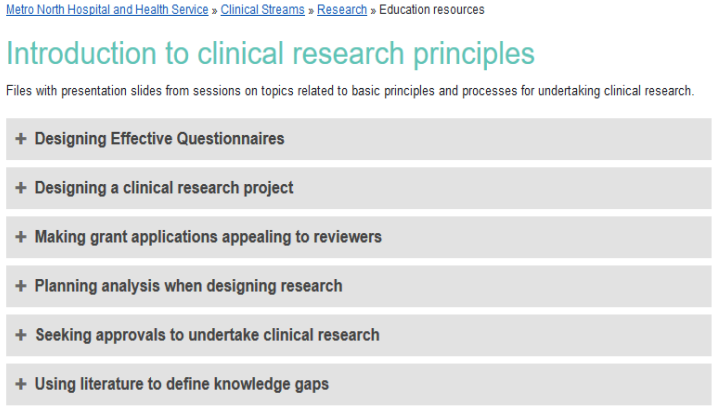
Clinical research education resources and tools

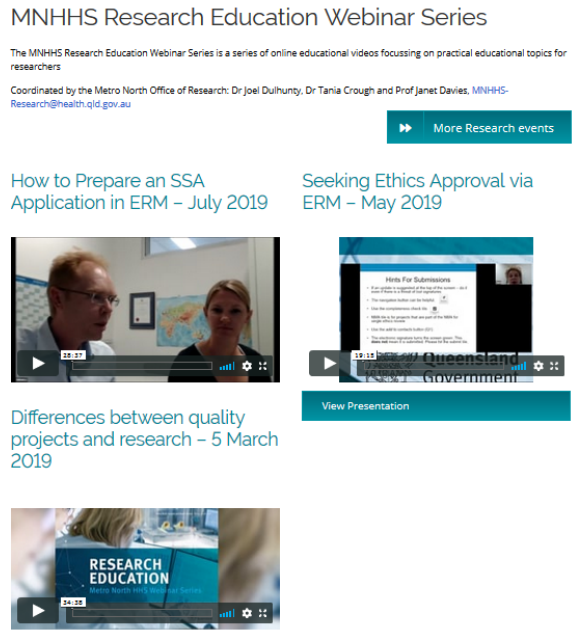
https://metronorth.health.qld.gov.au/research

https://qheps.health.qld.gov.au/metronorth/research/education-resources









Templates to assist research planning

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Tips!

***Follow all format and style instructions** provided by granting agency for the relevant scheme.*

***Adhere to length specified** and order sections as instructed.*

*Define all acronyms and **avoid over use of discipline-specific terms** and jargon. Your assessor may be outside your field.*

*Don't annoy a busy, over tired assessor with an overly long CV in tiny font that is hard to interpret- **make it easy for the assessor** to find the information about you that they need to know.*

*Include the sections that are **relevant to the scheme you are applying for** and use the headers and words asked for in their guidelines.*

***Align your CV** to reflect what the granter wants. Look at relevant successful examples if possible.*

Curriculum vitae

Name

Full professional title:

Contact email and phone number:

Position(s) / Affiliation(s)

(role title, % FTE, department):

Current and recent employment (roles/positions):

Institution and its location:

Education Qualifications

Degree(s), institute, year of award:

Career Interruptions

Indicate any (allowable for the grant scheme) career interruptions (eg for maternity, carer roles, health reasons) that have limited your clinical/research activity in the last (5 or 10) years. Indicate their duration and briefly outline their impact on your career and research productivity (see Metro North Procedure Research: Gender Equity (PROC004420), *NHMRC and ARC policies).*

Prof Janet Davies MNHHS-research@health.qld.gov.au MNHHS Office of Research

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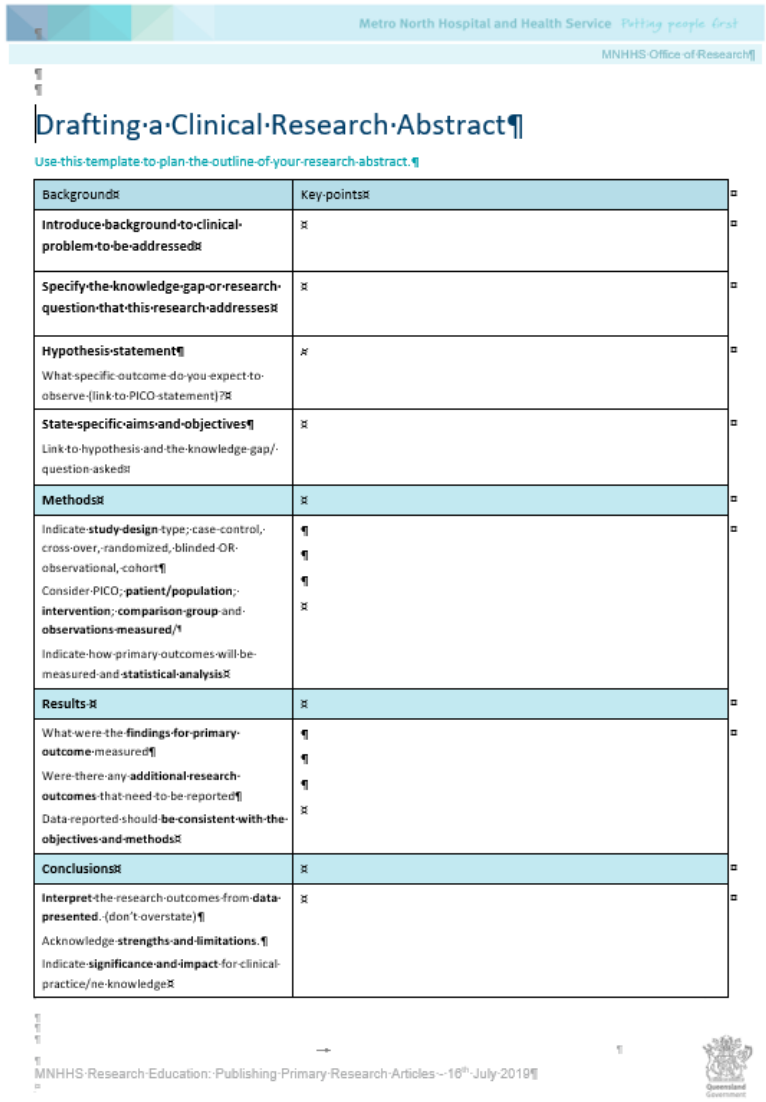
Moulding your first grant application

Use this template to brainstorm ideas for your application for research funding.

1) The scheme

Consideration	Your notes
The funding body	
Purpose of the funding body	
Who and what has been funded before?	*Homework: check funder website for previous successful application titles and awardees*
Scheme and purpose (e.g. scholarship, project, fellowship, priming grant)	
What can be supported? (budget items; salaries, lab research, consumables, external services, travel, memberships)	
What will not be supported? (some grants exclude travel, investigator salary or equipment)	
Application due date?	
Pre-approvals needed? (other investigators, Head of Department, Director or Chief Executive, HREC application number or HREC approval/ SSA)	

MNHHS Research Education: Moulding Your First Proposal – 18th July 2017



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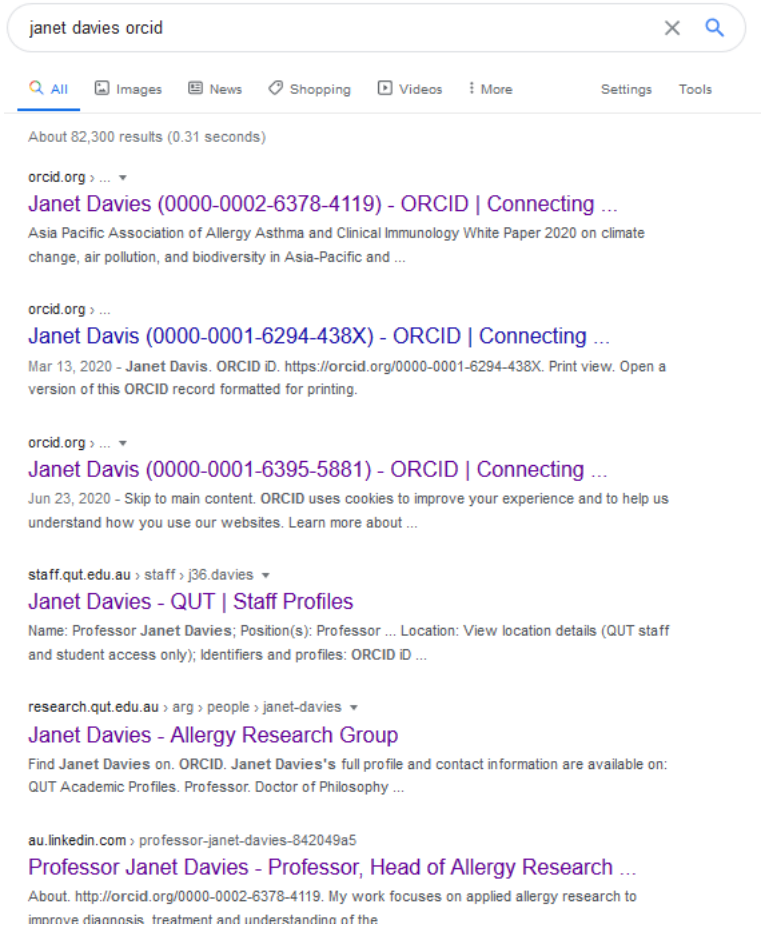
Drafting a Clinical Research Abstract

Use this template to plan the outline of your research abstract.

Background	Key points
Introduce background to clinical problem to be addressed	
Specify the knowledge gap or research question that this research addresses	
Hypothesis statement What specific outcome do you expect to observe (link to PICO statement)?	
State specific aims and objectives Link to hypothesis and the knowledge gap/ question asked	
Methods	
Indicate **study design** type; case-control, cross-over, randomized, blinded OR observational, cohort Consider PICO; **patient/population**; **intervention**; **comparison group** and **observations measured**/ Indicate how primary outcomes will be measured and **statistical analysis**	
Results	
What were the **findings for primary outcome** measured Were there any **additional research outcomes** that need to be reported Data reported should **be consistent with the objectives and methods**	
Conclusions	
Interpret the research outcomes from **data presented**. (don't overstate) Acknowledge **strengths and limitations.** Indicate **significance and impact** for clinical practice/ne knowledge	

MNHHS Research Education: Publishing Primary Research Articles – 16th July 2019

Become known as a researcher: ORCID



- Requested by publishers, funders, institutions (inc MNHHS; ROI)
- Links you with your funding, affiliations, outputs, &metrics
- Auto populated (once established), exportable
- Travels with you during your career

Basics of writing a primary research article

Core elements

- Abstract
- Introduction
- Materials and Methods
- Results
- Discussion
- Conclusions
- References

Other parts:

- Authors and affiliations
- Key words,
- Acknowledgements
- Funding agencies
- Conflicts of interests
- Author contributions

Process

- Online submission
- Full details of authors; Affiliations, qualifications
- Funding agencies
- Conflicts of interests
- Author contributions and approvals
- Upload files
- Suggest reviewers (sub-editor)
- Suggest who should not review (and why)
- Build PDF and approve submission
- Wait for editor decision
- Address reviewer comments and resubmit (same or new journal)
- (repeat if needed)
- Acceptance!

Target the right journal: Read the Guidelines

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GUIDE FOR AUTHORS

The Journal of Critical Care provides a forum for the publication of original peer-reviewed articles with the goal of improving patient care by integrating critical care systems knowledge into practice behavior. The journal represents the World Federation of Societies of Intensive and Critical Care Medicine (WFSICCM), an organization of 42 national intensive/critical care societies representing some 32,000 physicians and allied health professionals. With this responsibility to the WFSICCM comes an international focus in systems research in constrained resource environments.
We accept research articles and review articles as well as those in a seminar or tutorial format. Topics covered are all aspects of Health Services Research, the interface of critical care, anesthesiology, and pain, as well as tutorials for residency education core competencies.
For the seminar format, the articles should be directed to the resident or practicing healthcare professional. We are particularly interested in your up-to-date evaluation of the topic. Dealing with subjects of current and sometimes controversial educational and research themes is acceptable. The seminar format lends itself to a more informal presentation. Express your own viewpoints, but feel free to discuss other viewpoints as well. If you are uncertain, please indicate the degree of your uncertainty. We are looking for an absolutely honest evaluation of the topic.
Manuscripts are accepted for consideration on the condition that they are contributed solely to the Journal of Critical Care. No substantial part of a paper may have been or may be published elsewhere, except for an abstract of 200 words or less.
Manuscripts will be critically reviewed by the Editor with appropriate independent referees drawn from the Editorial Board and other experts. Acknowledgments to other investigators for advice or data must be substantiated by written authorization specifically granting permission to authors. Upon submission, authors will be required to fill out an ethics in publishing form. All submissions must also include a conflict of interest statement.

Submission checklist

You can use this list to carry out a final check of your submission before you send it to the journal for review. Please check the relevant section in this Guide for Authors for more details.

Ensure that the following items are present:

One author has been designated as the corresponding author with contact details:
- E-mail address
- Full postal address

All necessary files have been uploaded:
Manuscript:
- Include keywords
- All figures (include relevant captions)
- All tables (including titles, description, footnotes)
- Ensure all figure and table citations in the text match the files provided
- Indicate clearly if color should be used for any figures in print

Graphical Abstracts / Highlights files (where applicable)
Supplemental files (where applicable)

- What is the scope of the journal?
- Is the journal peer-reviewed?
- What is the impact factor for the journal?
  - Is it respected in your field?
  - Check reputation SciMago or library
  - (UQ /TPCH/Redcliff)
- If open access (how much $$$), is it reputable?

Read published examples to guide style and fit for your research

- https://www.scimagojr.com/journalrank.php

Structuring the draft 1.

- Background/ Introduction
  - Introduce the clinical problem (scale; health, social, economic impact)
  - Provide focused summary of current relevant knowledge
  - Identify knowledge gaps that your research will address
  - Pose the critical question
  - State Hypothesis, aims and objectives
- Methods
  - Summarise study design (refer to published protocol, if relevant)
  - Identify patient population(s); inclusion and exclusion criteria; control group
  - Detail methods/intervention so a skilled researcher in field could replicate the study
  - Specify how primary (and secondary) outcome will be measured
  - Outline statistical analysis plan

Structuring the draft 2.

Results

- Report information on participants recruited to the study; allocation to study arms
- Present data as described in protocol; tabulate or graph data
- Focus on primary outcome measures
- Were the primary outcomes significant by test specified in protocol (and clinically meaningful)?
- Describe other outcomes, findings, observations

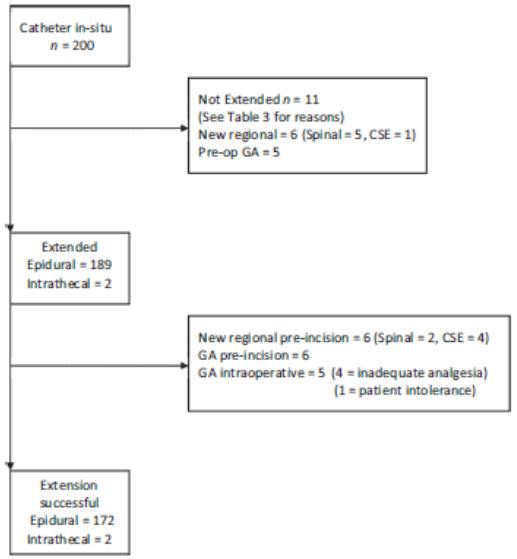


Table 1
Univariable analysis of patients receiving piperacillin/tazobactam versus patients receiving meropenem.

Variable	TZP ($n = 205$)	MER ($n = 48$)	p-value
Age (yr), mean, SD	62.4 (15.5)	63 (12.7)	0.781
Gender, male (%)	129 (62.9%)	35 (72.9%)	0.192
Weight (kg), mean, SD	74.6 (16.1)	82.8 (18.7)	0.006
Height (cm), mean, SD	170.3 (15.1)	173 (9.8)	0.125
APACHE II, mean, SD	22.9 (8.1)	26 (9.3)	0.036
SOFA, median, IQR	4 (0–8)	7 (3—11)	0.005
Serum creatinine (mg/dL), median, IQR	0.8 (0.6–1.2)	0.8 (0.5–1.1)	0.371
CL_{CR} (mL/min), mean, SD	102.1 (63.3)	89.3 (82.4)	0.347
Estimated creatinine clearance (mL/min), mean, SD	95.4 (58.3)	117.8 (68.2)	0.034
Vasopressive therapy, yes (%)	0%	2.1%	0.093
Fluid balance (mL), mean, SD	1303.9 (1751.1)	1549.5 (1882.9)	0.413

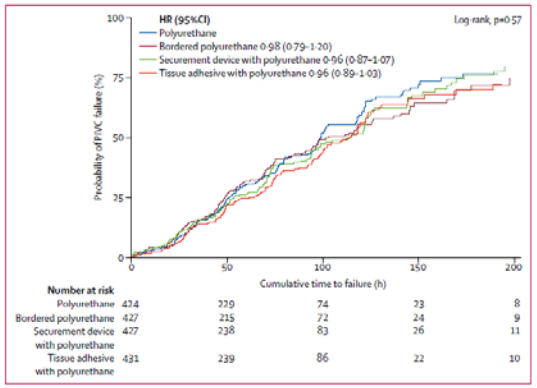


Figure 3: Kaplan–Meier analysis of survival from device failure
X-axis is truncated at 200 h.

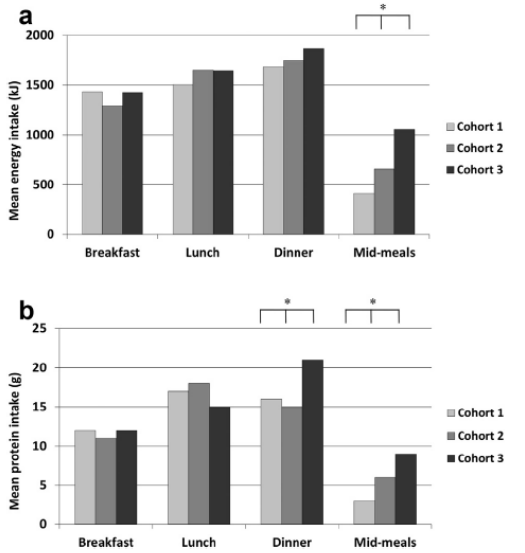


Fig. 3. a. Comparison of mean energy intake of cohort 1 (n = 129), cohort 2 (n = 139) and cohort 3 (n = 52), by meal. *p < 0.001 (one-way ANOVA). b. Comparison of mean protein intake of cohort 1 (n = 129), cohort 2 (n = 139) and cohort 3 (n = 52), by meal. *p < 0.001 (one-way ANOVA).

Discussion and Conclusion

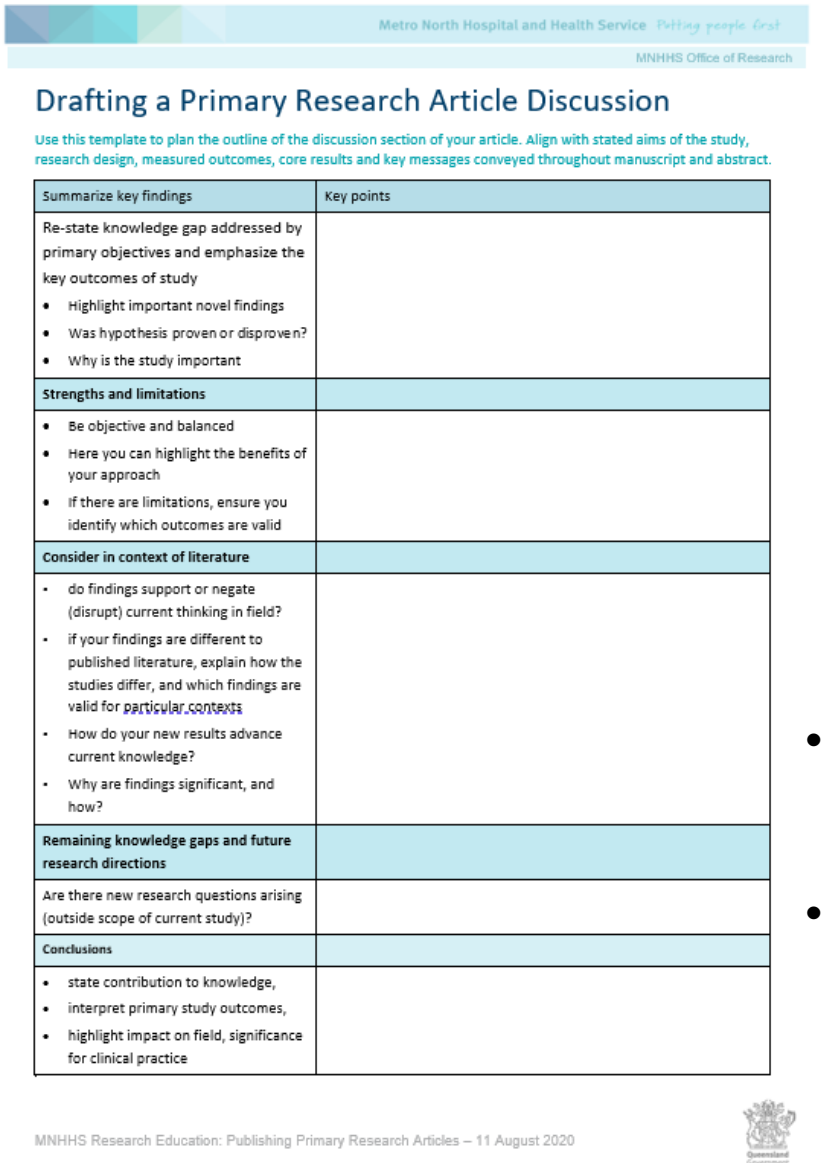
1. Re-state knowledge gap addressed by primary objectives and emphasize the key outcomes of study
    - highlight novel findings
    - Was hypothesis proven or disproven?
2. Consider technical strengths and limitations of the study (objectively)
3. Critically consider findings in the context of other studies;
    - do findings support or negate current thinking in field?
    - if your findings are different to published literature, explain how the studies differ, and which finding(s) is/are valid for particular context(s)
    - How do your new results advance current knowledge?
    - Why are the findings significant and how?
4. Identify remaining knowledge gaps and future research directions
5. Conclude: state contribution to knowledge, interpret primary study outcomes, and significance for clinical practice

- Harmonize messages and flow across the whole manuscript;

→ background, aims, study design, methods, outcomes measured, results and interpretation

- Ensure the conclusions are supported by data (*overstating outcomes is a door closer*)
- Be up front about strengths as well as any limitations (*or your reviewer will*)
- Clearly convey meaning, impact in your field and significance
- **What's the hook for the editor?**
- You can talk up the article a little in the cover letter, but be real in the manuscript

Publishing Primary Research Articles Discussion template



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Drafting a Primary Research Article Discussion

Use this template to plan the outline of the discussion section of your article. Align with stated aims of the study, research design, measured outcomes, core results and key messages conveyed throughout manuscript and abstract.

Summarize key findings	Key points
Re-state knowledge gap addressed by primary objectives and emphasize the key outcomes of study • Highlight important novel findings • Was hypothesis proven or disproven? • Why is the study important	
Strengths and limitations	
• Be objective and balanced • Here you can highlight the benefits of your approach • If there are limitations, ensure you identify which outcomes are valid	
Consider in context of literature	
• do findings support or negate (disrupt) current thinking in field? • if your findings are different to published literature, explain how the studies differ, and which findings are valid for particular contexts • How do your new results advance current knowledge? • Why are findings significant, and how?	
Remaining knowledge gaps and future research directions	
Are there new research questions arising (outside scope of current study)?	
Conclusions	
• state contribution to knowledge, • interpret primary study outcomes, • highlight impact on field, significance for clinical practice	

MNHHS Research Education: Publishing Primary Research Articles – 11 August 2020

- Word version will be made available on QHEPS Metro North Research Education Resources webpage
- And circulated to participants with feedback form

blood®

Plenary Paper

MYELOID NEOPLASIA

Jak2V617F and Dnmt3a loss cooperate to induce myelofibrosis through activated enhancer-driven inflammation

Sebastien Jacquelin,[1] Jasmin Straube,[1] Leanne Cooper,[1] Therese Vu,[1] Axia Song,[1] Megan Bywater,[1] Eva Baxter,[1] Matthew Heidecker,[1] Brad Wackrow,[1] Amy Porter,[1] Victoria Ling,[1] Joanne Green,[1] Rebecca Austin,[1] Stephen Kazakoff,[1] Nicola Waddell,[1] Luke B. Hesson,[2,3] John E. Pimanda,[2,4,5] Frank Stegelmann,[6] Lars Bullinger,[7] Konstanze Döhner,[6] Raajit K. Rampal,[8] Dirk Heckl,[9] Geoffrey R. Hill,[1,10,11] and Steven W. Lane[1,10,11]

[1]QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia; [2]The Prince of Wales Clinical School, Lowy Cancer Research Centre, UNSW Sydney, Sydney, NSW, Australia; [3]Kinghorn Centre for Clinical Genomics, Garvan Institute of Medical Research, Darlinghurst, NSW, Australia; [4]Department of Pathology, School of Medical Sciences, UNSW Sydney, Sydney, NSW, Australia; [5]Department of Haematology, Prince of Wales Hospital, Randwick, NSW, Australia; [6]Department of Internal Medicine III, University Hospital of Ulm, Ulm, Germany; [7]Department of Hematology, Oncology, and Tumorimmunology, Charité University Medicine, Berlin, Germany; [8]Leukemia Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; [9]Department of Pediatric Hematology and Oncology, Hannover Medical School, Hannover, Germany; [10]The Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia; and [11]School of Medicine, University of Queensland, Brisbane, QLD, Australia

KEY POINTS

- **Loss of Dnmt3a in hematopoietic stem cells cooperates with Jak2V617F to induce lethal myelofibrosis.**
- **Dnmt3a loss leads to activation of enhancers and drives aberrant self-renewal and inflammatory signaling.**

Myeloproliferative neoplasms (MPNs) are a group of blood cancers that arise following the sequential acquisition of genetic lesions in hematopoietic stem and progenitor cells (HSPCs). We identify mutational cooperation between Jak2V617F expression and Dnmt3a loss that drives progression from early-stage polycythemia vera to advanced myelofibrosis. Using in vivo, clustered regularly interspaced short palindromic repeats (CRISPR) with CRISPR-associated protein 9 (Cas9) disruption of Dnmt3a in Jak2V617F knockin HSPC, we show that Dnmt3a loss blocks the accumulation of erythroid elements and causes fibrotic infiltration within the bone marrow and spleen. Transcriptional analysis and integration with human data sets identified a core DNMT3A-driven gene-expression program shared across multiple models and contexts of Dnmt3a loss. Aberrant self-renewal and inflammatory signaling were seen in Dnmt3a$^{-/-}$ Jak2V617F HSPC, driven by increased chromatin accessibility at enhancer elements. These findings identify oncogenic cooperativity between Jak2V617F-driven MPN and Dnmt3a loss, leading to activation of HSPC enhancer–driven inflammatory signaling. (*Blood.* 2018;132(26):2707-2721)

conclusions limited to reported outcomes

Blood

Peer-reviewed journal

Blood is a peer-reviewed medical journal published by the American Society of Hematology. It was established by William Dameshek in 1946. The journal changed from semimonthly to weekly publication at the start of 2009. Wikipedia

Impact factor: 16.601 (2018)

Editor: Nancy Berliner

First issue date: 1946

Discipline: Hematology

OCLC number: 01536582

https://pubmed.ncbi.nlm.nih.gov/30366920/
doi: 10.1182/blood-2018-04-846220

ure 7A). We observed close correlation
the 41 920 total annotated enhancer
-seq peaks (30 863 marks). Most of the
ed with active 2762 (88.9%) or primed
arks (supplemental Figure 7A,C). There
: of gained peaks at active enhancers
b) of Jak2^{VF}-Dnmt3a-Cas9 upregulated
28) (Figure 7B,D; supplemental Table 4,
ntial peaks). Only a small proportion of
mt3a-Cas9 g
arks (supplemental Figure 7D; Figure 7C).
demonstrate that loss of Dnmt3a leads
accessibility
drives HSC g

lidate these findings in the context of
ancies with mutant DNMT3A. We ex-
e expression and chromatin accessibil-
Cs (pHSCs).[47] pHSCs resemble normal
notype (CD34$^+$CD38$^-$CD99$^-$Tim3$^-$) and
der leukemogenic mutations (including
l on a cohort of DNMT3A mutant and
– 5 vs 6) with fully annotated ATAC-seq
ata.[47] Gene expression from DNMT3A
ted with the transcri
t3a-Cas9 HSCs (Figu
chment score [NES] –
NES – –2, FDR – 0.001), demonstrating
SC model to our Dnmt3a-Jak2^{VF} model.
of chromatin accessibility in DNMT3A
ed with DNMT3A WT pHSC controls,
aracterized active an
4$^+$ cells (Figure 7F),
o human disease.

ises inflammation

it significantly elevated levels of proin-
hat contribute to fibrosis and this is as-
prognosis.[9,48] Jak2^{VF}-Dnmt3a-Cas9 LSKs
nment for inflammatory pathways, spe-
factor α (TNFα), even though these mice
velop MF for many mor
naling is a consistent,
dels including mice with a constitutively
nutation,[49] and MF driven by EZH2 loss
NFα signaling was driven by pathologic
hancer loci within Jak2^{VF}-Dnmt3a-Cas9
ed by 46 of the 68 upregulated genes
) showing increased DNA accessibility
supplemental Table 5; supplemental
a-Cas9 LSK and LT
alidating these findings (Figure 7I). TF
ormed on patients with MF with mutated
d controls. DNMT3A mutated MF sam-
chment of inflammatory TNFα pathways
with the gene-expression changes seen
a-Cas9 HSCs, thus validating our findings
disease (Figure 7I-J). Altogether, these
h Dnmt3a loss of function leading to
of enhancer elements that drive MF
α signaling and proinflammatory gene
bstract).

Discussion

The long-term survival of most patients with PV and ET is excellent.[8] In contrast, advanced MPNs such as MF or AML causes substantial morbidity and has a dramatic negative impact on survival.[5-8] Understanding the factors that contribute to myelofibrotic transformation of MPNs is essential to identify patients early for clinical trials, and to develop treatments that prevent or reverse these processes in patients. We used CRISPR/Cas9 technology to induce cooperating lesions in Dnmt3a in the Jak2^{VF}-induced PV model, leading to fully penetrant MF. This method is highly efficient, can be used to edit HSCs in vivo, and may be extended to test the effects of other secondary mutations commonly found in transformed MPNs such as TP53, EZH2, or ASXL1.[10,51] Our work thereby establishes a platform to sequentially examine the effects of novel mutations on MPN disease biology and response to treatment. We observed excellent correlation between the transcriptional effects of Dnmt3a loss[22-26] by CRISPR vs genetic deletion of Dnmt3a or mutant Dnmt3a expression, and this also correlates with phenotypic changes (differentiation block and gain of stem cell identity). These results show that de novo mutation acquisition in Jak2^{VF} MPN-driven pathology can modify HSC biology and lead to disease evolution. In vitro Dnmt3a editing was sufficient to immortalize LSK, and enriched for HSC phenotypic markers and gene expression. However, the overall transcriptional program induced by in vitro Dnmt3a loss did not reproduce the findings from other models, or from patients, suggesting that extrinsic signals from the proinflammatory microenvironment contribute to the development of MF,[52,53] further evidenced by the depletion of nonedited Jak2^{VF} LT-HSCs in myelofibrotic recipients (Figure 4B). Altogether, this work demonstrates the power of in vivo CRISPR/Cas9 genomic editing to faithfully recapitulating the findings of human disease in a murine system.

In vivo deletion of Dnmt3a in HSCs using CRISPR/Cas9 induced a dominant transcriptional signature that closely reflected other genetically engineered mouse models and primary human leukemia and advanced-stage MPNs. Genome wide DNA methylation changes did not show such close overlap between studies, nor did it explain the majority of transcriptional changes. This led us to hypothesize that the Dnmt3a was acting predominantly through the regulation of chromatin topology and methylation of specific chromatin marks. Using ATAC-seq on in vivo–edited HSC populations, we were able to demonstrate a widespread increase in chromatin accessibility at active enhancers that have been shown to regulate HSC gene expression.[29,32,44,45]

These data, across distinct clinical contexts and models, show that DNMT3A mutant blood cancers are "enhanceropathies," driven by reproducible transcriptional programs downstream of enhancer activation. The mechanism of this pathologic enhancer activation appears to be through the failure to convert active enhancers to the repressive H3K27me3 marks. This is an important step in developmental biology and is critical in silencing the stemness program during differentiation.[54] H3K27Ac and H3K27me3 are mutually exclusive[55] and the PRC2 complex, together with histone acetyltransferases p300 and CBP, regulate this conversion.[56,57] The direct interaction between PRC2 and WT or mutant Dnmt3a remain active research questions of interest.[58] Loss of DNMT3A induces focal hypomethylation,

decreases PRC2 recruitment at H3K27 favoring the maintenance of an acetylation mark, and leads to sustained enhancer activation, and persistent stem cell gene expression. We found that increased chromatin accessibility was not restricted to enhancer loci associated with activated genes, and therefore additional factors may also contribute to disease progression.

Alterations within cis-acting regulatory elements can drive MPN-associated inflammation via constitutive activation of NF-κB signaling,[49,50] and, more broadly, constitutive NF-κB pathway activation has been reported in AML.[59,60] We found that Dnmt3a loss of function is associated with strong enrichment of TNFα via NF-κB pathways, again driven by increased chromatin accessibility and pathologic enhancer activation, leading to MF. These data are analogous to the changes seen with Ezh2 loss in Jak2V617F MF, and suggest a common epigenetic mechanism of MF transformation from early-stage MPNs, mediated by inflammatory signaling. This has additional therapeutic relevance, as bromodomain inhibitors have remarkable activity in the context of enhancer activation.[49,61]

We postulate an important role of TNFα and inflammatory cytokine signaling following Dnmt3a loss in Jak2^{VF} MPNs, consistent with other reports.[62] In patients with JAK2^{VF} PV, DNMT3A mutations appear to be associated with lack of response to pegylated interferon α and many patients may actually acquire a DNMT3A mutation during interferon treatment.[63] Furthermore, in the context of other potent oncogenes that activate tyrosine kinase signaling pathways, such as NRas[32] and FLT3^{ITD}[15,24], DNMT3A mutations drive resistance to common chemotherapy agents.[24] This CRISPR-mediated combinatorial model provides a scalable and tractable opportunity to evaluate the effects of specific therapies on Jak2^{VF} HSCs that contain additional genetic lesions associated with progression to post-PV MF or AML.

Overall, this work demonstrates the power of in vivo CRISPR-Cas9 gene editing to model disease progression and oncogene cooperativity in vivo. Mechanistically, Dnmt3a loss accelerated Jak2^{VF} MPNs through aberrant stem cell and inflammatory gene expression and the failure to silence developmentally active stem cell enhancers. Such knowledge has the potential to shape the development of targeted therapeutic approaches in transformed MPNs, a highly chemorefractory disease associated with poor prognosis. This work reinforces the prognostic relevance of the genetic landscape of MPNs at diagnosis and as these genetic changes evolve over time. Finally, these data also support clinical trials to test whether genetic profiling can be used to prospectively select high-risk patients for alternate clinical management to prevent progression to transformed MPNs.

Acknowledgments

The authors are grateful for the discussions and he
colleagues including Stacey Edwards, Juliet Frenc
Mark Smyth, Ann Mullally, Michael Milsom, and F
thors acknowledge support from the flow cytome
Chojnowski), animal facility, and support divisio

This work was supported by the Cancer Australia
Foundation (1124096) and the Gordon and Jessie
search Trust. S.W.L. is a CSL Centenary Fellow and
Health and Medical Research Council (NHMRC) supp
and support from the MPN Research Foundation/
G.R.H. is an NHMRC Senior Principal Research fel
by the German Cancer Aid (111743). J.E.P. is sup
1139811) and The T
Institute of NSW and

Authorship

Contribution: S.J. conceptualized the study, de
formed experiments, analyzed the results, and wro
performed bioinformatics analysis; L.C., T.V., A.S.,
J.G., V.L., and R.A. performed experiments; E.B
methodology and obtained resources; S.K. and
study; L.B.H. designed experiments; J.E.P. devel
K.R. collected, an
eviewed the man
resources and designed the research; G.R.H. va
designed the research; and S.W.L. supervised th
research, and wrote the manuscript.

Conflict-of-interest disclosure: The authors dec
nancial interests.

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Submitted 25 April 2018; accepted 17 Octobe
online as *Blood* First Edition paper, 26 Octobe
blood-2018-04-846220.

The online version of this article contains a data

There is a *Blood* Commentary on this article in th

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The Problem

The objecti ve

The appraoch

The advantage/ point of difference

qualification/ limitation?

significance

interpretation

framing in context of literature

clinical relevance

what is known

outcome

what is novel and how it fits in

external validation

implications

conclusion

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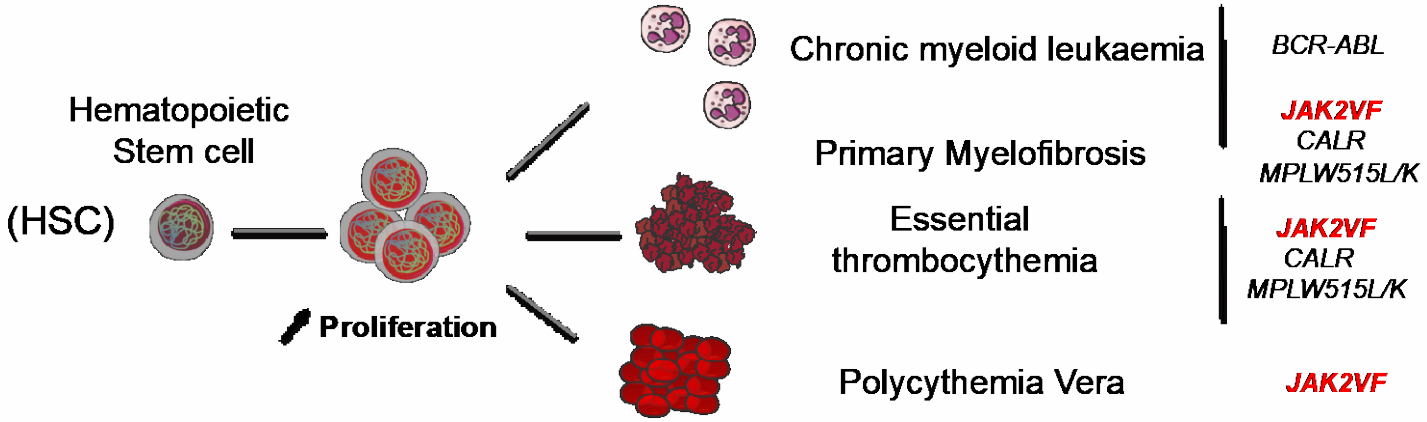
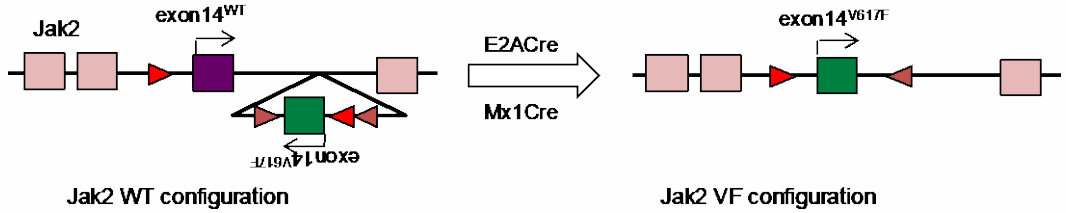
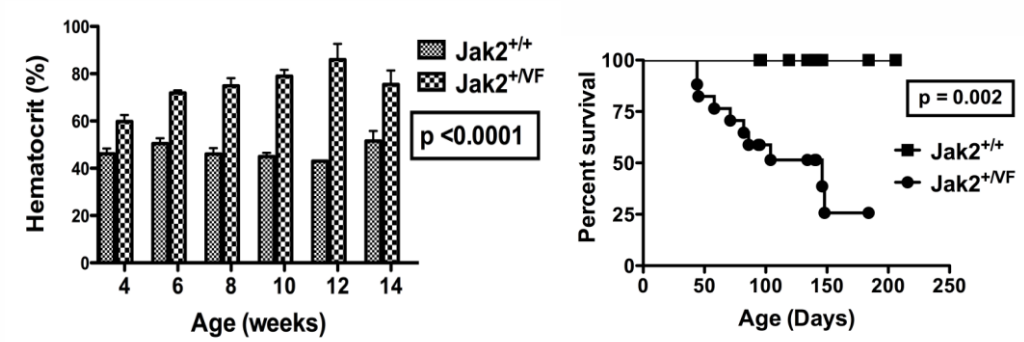
MNHHS research seminar
11 Aug 2020

Modeling disease progression in MPN using CRISPR-Cas9





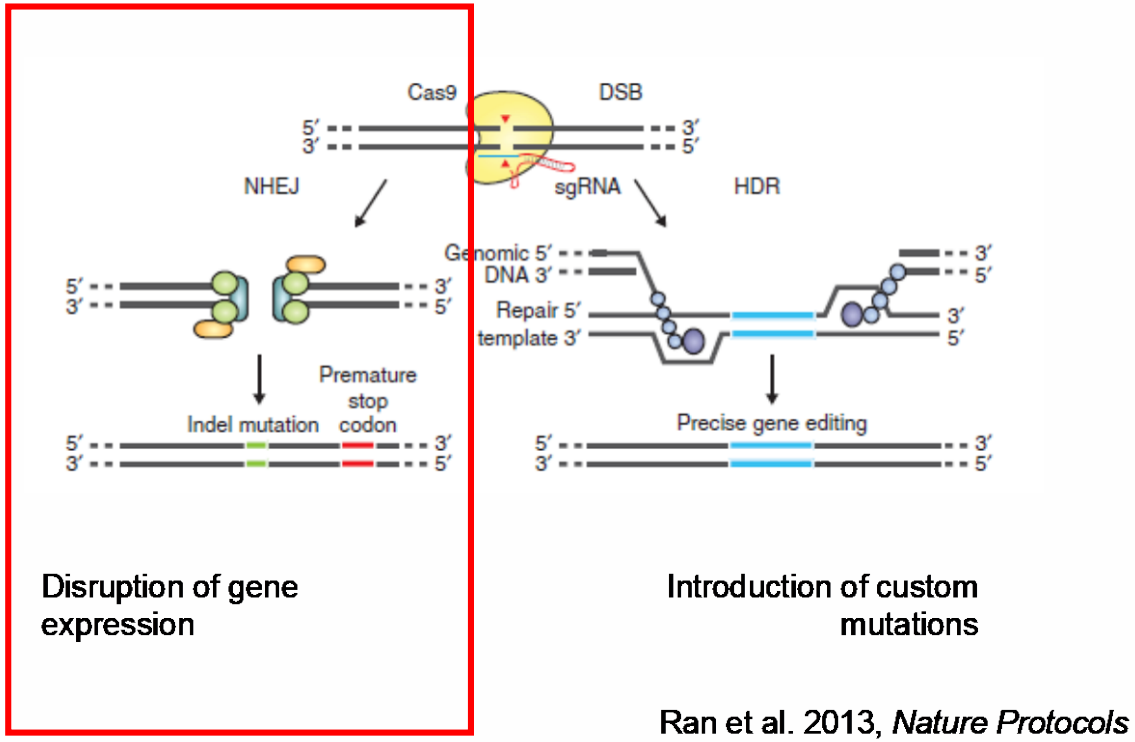


Cancer Cell, 2010

- ✓ "Modifier" secondary mutations arise within MPN stem cells
- ✓ Epigenetic pathway genes (DNMT3A, EZH2, ASXL1) are the most frequently mutated group of non kinase mutations
- ✓ The presence of additional mutations has a powerful, negative effect on prognosis

Tefferi, Pardanani, Blood Advances 2016

Modeling disease progression in MPN using CRISPR-Cas9

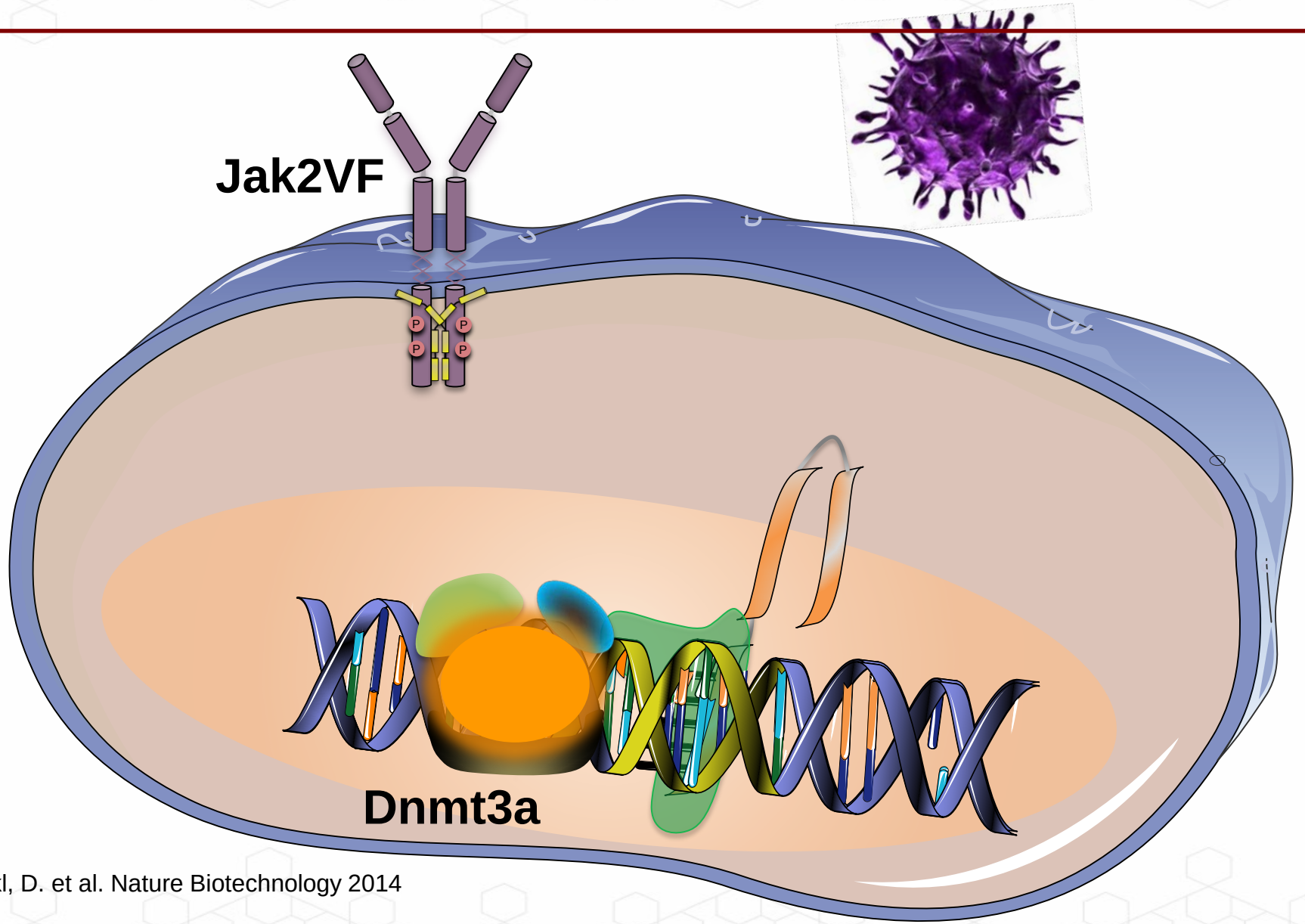


Disruption of gene expression

Introduction of custom mutations

Ran et al. 2013, *Nature Protocols*

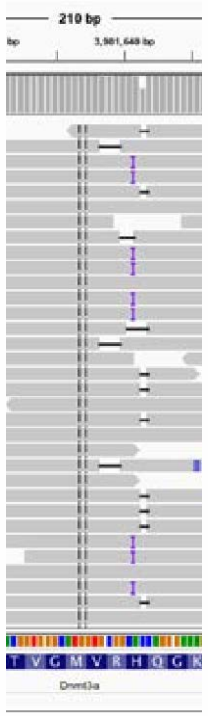
Lentivirus-delivered CRISPR-Cas9 editing to modulate Dnmt3a activity

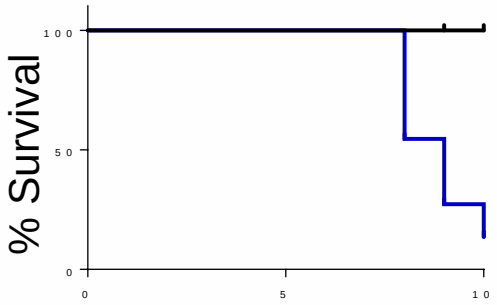


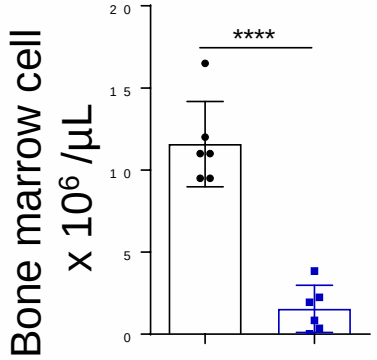
Sebastien Jacquelin

Heckl, D. et al. Nature Biotechnology 2014

Jak2VF ΔDnmt3a cooperates to induce lethal myelofibrosis



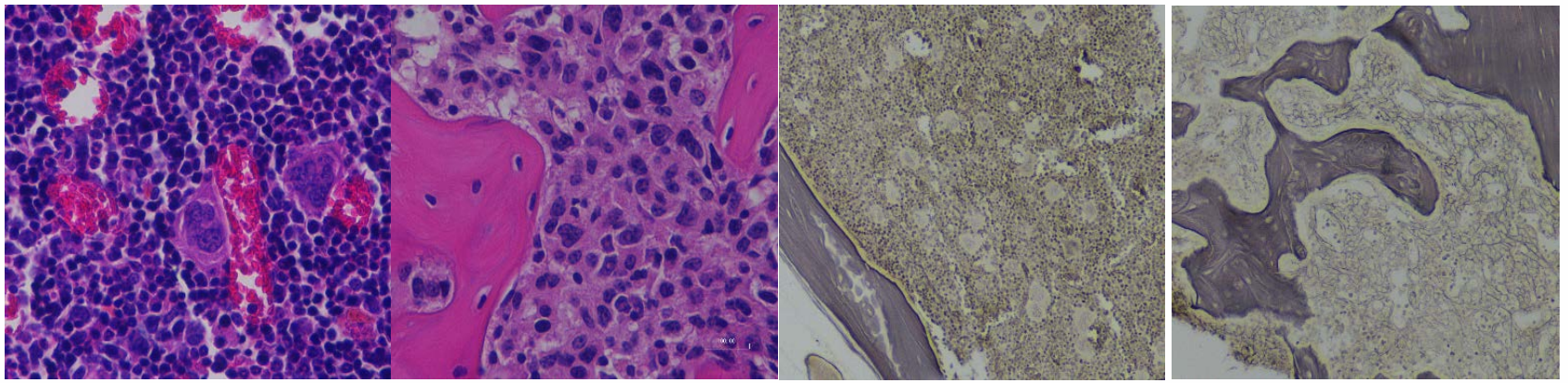




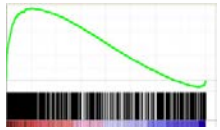
Jak2VF-cas9

Jak2VF-Dnmt3a-cas9

Jak2VF-cas9 | **Jak2VF-Dnmt3a -cas9** | **Jak2VF-cas9** | **Jak2VF-Dnmt3a -cas9**



This model can be used to understand human disease, demonstrates increased inflammatory singaling pathways – a new target in myelofibrosis



Clinical Infectious Diseases

MAJOR ARTICLE

The Effect of Renal Replacement Therapy and Antibiotic Dose on Antibiotic Concentrations in Critically Ill Patients: Data From the Multinational Sampling Antibiotics in Renal Replacement Therapy Study

Jason A. Roberts,[1,2,3,4] Gavin M. Joynt,[5] Anna Lee,[5] Gordon Choi,[5] Rinaldo Bellomo,[6] Salmaan Kanji,[7,8] M. Yugan Mudaliar,[9,10] Sandra L. Peake,[11,12,13] Dianne Stephens,[14,15,16] Fabio Silvio Taccone,[17] Marta Ulldemolins,[18,19,20] Miia Maaria Valkonen,[21] Julius Agbeve,[22] João P. Baptista,[23] Vasileios Bekos,[24] Clement Boidin,[1,25,26] Alexander Brinkmann,[27] Luke Buizen,[28] Pedro Castro,[29,30] C. Louise Cole,[10,31] Jacques Creteur,[17] Jan J. De Waele,[32] Renae Deans,[1] Glenn M. Eastwood,[6] Leslie Escobar,[33] Charles Gomersall,[5] Rebecca Gresham,[31] Janattul Ain Jamal,[34] Stefan Kluge,[35] Christina König,[35,36] Vasilios P. Koulouras,[37] Melissa Lassig-Smith,[2] Pierre-Francois Laterre,[38] Katie Lei,[29] Patricia Leung,[5] Jean-Yves Lefrant,[40] Mireia Llauradó-Serra,[41] Ignacio Martin-Loeches,[18,42] Mohd Basri Mat Nor,[43] Marlies Ostermann,[29] Suzanne L. Parker,[1] Jordi Rello,[44] Darren M. Roberts,[1] Michael S. Roberts,[45,46,47] Brent Richards,[48] Alejandro Rodriguez,[49,50] Anka C. Roehr,[51] Claire Roger,[40] Leonardo Seoane,[52,53] Mahipal Sinnollareddy,[45,46] Eduardo Sousa,[23] Dolors Soy,[30,54] Anna Spring,[24] Therese Starr,[2] Jane Thomas,[14] John Turnidge,[12] Steven C. Wallis,[1] Tricia Williams,[11,12,13] Xavier Wittebole,[38] Xanthi T. Zikou,[55] Sanjoy K. Paul,[28] Jeffrey Lipman[1,2]; on behalf of the SMARRT Study Collaborators and the ANZICS Clinical Trials Group[a]

Background. The optimal dosing of antibiotics in critically ill patients receiving renal replacement therapy (RRT) remains unclear. In this study, we describe the variability in RRT techniques and antibiotic dosing in critically ill patients receiving RRT and relate observed trough antibiotic concentrations to optimal targets.

Methods. We performed a prospective, observational, multinational, pharmacokinetic study in 29 intensive care units from 14 countries. We collected demographic, clinical, and RRT data. We measured trough antibiotic concentrations of meropenem, piperacillin-tazobactam, and vancomycin and related them to high- and low-target trough concentrations.

Results. We studied 381 patients and obtained 508 trough antibiotic concentrations. There was wide variability (4–8-fold) in antibiotic dosing regimens, RRT prescription, and estimated endogenous renal function. The overall median estimated total renal clearance (eTRCL) was 50 mL/minute (interquartile range [IQR], 35–65) and higher eTRCL was associated with lower trough concentrations for all antibiotics ($P < .05$). The median (IQR) trough concentration for meropenem was 12.1 mg/L (7.9–18.8), piperacillin was 78.6 mg/L (49.5–127.3), tazobactam was 9.5 mg/L (6.3–14.2), and vancomycin was 14.3 mg/L (11.6–21.8). Trough concentrations failed to meet optimal higher limits in 26%, 36%, and 72% and optimal lower limits in 4%, 4%, and 55% of patients for meropenem, piperacillin, and vancomycin, respectively.

Conclusions. In critically ill patients treated with RRT, antibiotic dosing regimens, RRT prescription, and eTRCL varied markedly and resulted in highly variable antibiotic concentrations that failed to meet therapeutic targets in many patients.

Keywords. pharmacokinetic; continuous renal replacement therapy; extended daily dialysis; beta-lactam; renal clearance.

Clinical Infectious Diseases

Peer-reviewed journal

Clinical Infectious Diseases is a peer-reviewed medical journal published by Oxford University Press covering research on the pathogenesis, clinical investigation, medical microbiology, diagnosis, immune mechanisms, and treatment of diseases caused by infectious agents. Wikipedia

Impact factor: 9.117 (2017)

ISSN: 1058-4838 (print); 1537-6591 (web)

ISO 4: Clin. Infect. Dis

History: 1979-present

CODEN: CIDIEL

Editor: Robert T. Schooley

https://pubmed.ncbi.nlm.nih.gov/32150603/

DOI: 10.1093/cid/ciaa224

DISCUSSION

Key Findings

In this large, prospective, multinational study, we found highly variable modes and intensity of RRT prescription with up to an 8-fold variability in eTRCL. Similarly, antibiotic dosing regimens demonstrated up to 8-fold variability in daily dose. The above factors led to highly variable trough antibiotic concentrations with failure to achieve higher therapeutic target concentrations in a substantial number of patients (≥25%). Similarly, the lower therapeutic target was not delivered in up to 55% of patients receiving vancomycin, and excessive antibiotic concentrations occurred with moderate frequency. We also observed higher mortality rates for patients receiving B-lactam (meropenem or piperacillin) or vancomycin therapy when less than 1× MIC or very high concentrations were present. Finally, our estimate of total combined RRT and renal clearance,

1500 mg every 12 h	2 (3.2)	19.6 (15.7–NR)
1500 mg every 24 h	5 (8.1)	11.8 (10.3–22.3)
2000 mg every 12 h	1 (1.6)	13.6 (13.6–13.6)
2000 mg every 24 h	2 (3.2)	12.2 (8.2–NR)

Abbreviations: IQR, interquartile range; NR, not reported.

eTRCL, was generally inversely associated with trough antibiotic concentrations, while other potentially influential factors (SOFA score and serum albumin concentration) showed no associations with trough concentration.

Relationship to Previous Studies

Variability in RRT prescription was not unexpected [20]; however, the broad distribution of dosing regimens was marked and aligns with a previous smaller multicenter study [31]. Similarly, smaller studies have hypothesized that critically ill patients receiving RRT may inconsistently achieve therapeutic drug exposures. A single-center study reported that 35% of critically ill

Although not a primary objective of this study, we observed associations of patient survival with the achievement of either therapeutic B-lactam (either meropenem or piperacillin) or tazobactam exposure. Interestingly, high drug exposures were associated with a higher likelihood of death, presumably because a higher severity of illness means higher organ failure, which, in turn, leads to decreased elimination of antibiotics and hence higher trough concentrations. A similar effect has been reported previously [38, 39]. The interaction between therapeutic antibiotic exposure and clinical cure and/or survival has been described previously [40, 41], although not in this patient population. These data may be useful for guiding design of therapeutic targets for future dosing intervention studies in critically ill patients receiving RRT.

Implications

Our analysis demonstrates that current practice in RRT prescription and antibiotic dosing has great variability and often results in inadequate or potentially toxic trough concentrations in a substantial number of patients. Moreover, despite demonstrating statistical correlations between dose and eTRCL with trough concentrations, our findings imply that accurately predicting dosing requirements based on eTRCL is currently impossible. No RRT prescription or dosing regimen could reliably be considered to enable more consistent achievement of target exposures. Indeed, TDM should be applied, where available, to avoid harm from both, undertreatment and toxicity [42, 43].

Strengths and Weaknesses

This is the largest pharmacokinetic study in critically ill patients receiving RRT. In all patients, RRT prescriptions and antibiotic dosing regimens were determined by treating clinicians, providing a pragmatic view of the variability of international clinical practice. The comparison of funded and nonfunded datasets revealed minor differences, with the exception of vancomycin trough concentrations. The lower concentrations in the nonfunded cohort reflect the higher usage of PIRRT in this subgroup. Nevertheless, the overall dataset combining data from studies with substantially similar methodology greatly increased the available data from various modes and intensities of RRT and ensured achievement of optimal sample sizes for piperacillin and meropenem. Although the target sample size was not achieved, this study provides one of the largest vancomycin datasets available for this patient group. The estimation of eTRCL has limitations, particularly when predilution flow rates are high. Although optimal antibiotic concentration targets are not definitively known, the targets chosen are the most widely accepted [29, 44], and they provide a marker against which local antibiotic MIC values can be compared.

Conclusions

In a multicenter pragmatic pharmacokinetic study of antibiotic therapy during RRT in critically ill patients, we found considerable variation in RRT prescription and antibiotic dosing resulting in subtherapeutic or excessive antibiotic concentrations in many patients. We also found no close and consistent associations between trough antibiotic concentration and dosage choice, acute physiological disturbance, eTRCL, and markers of protein binding such as albumin concentration, demonstrating the difficulty in ensuring target antibiotic concentrations. These findings highlight the need to improve our understanding of

Clinical Infectious Diseases

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Methods

- Study Design
  - PK Sampling
  - Microbiological testing
  - Defining therapeutic concentrations

Results

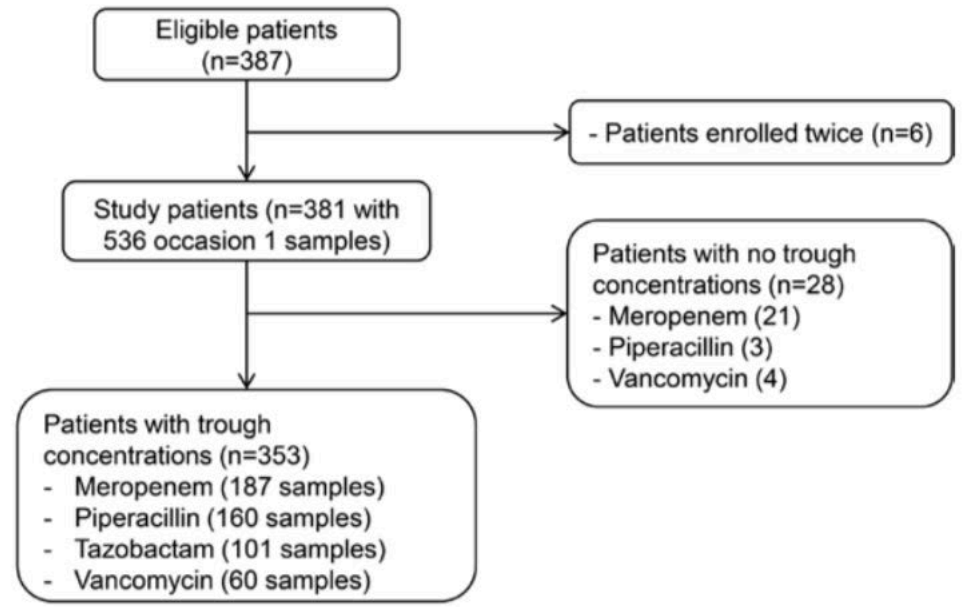
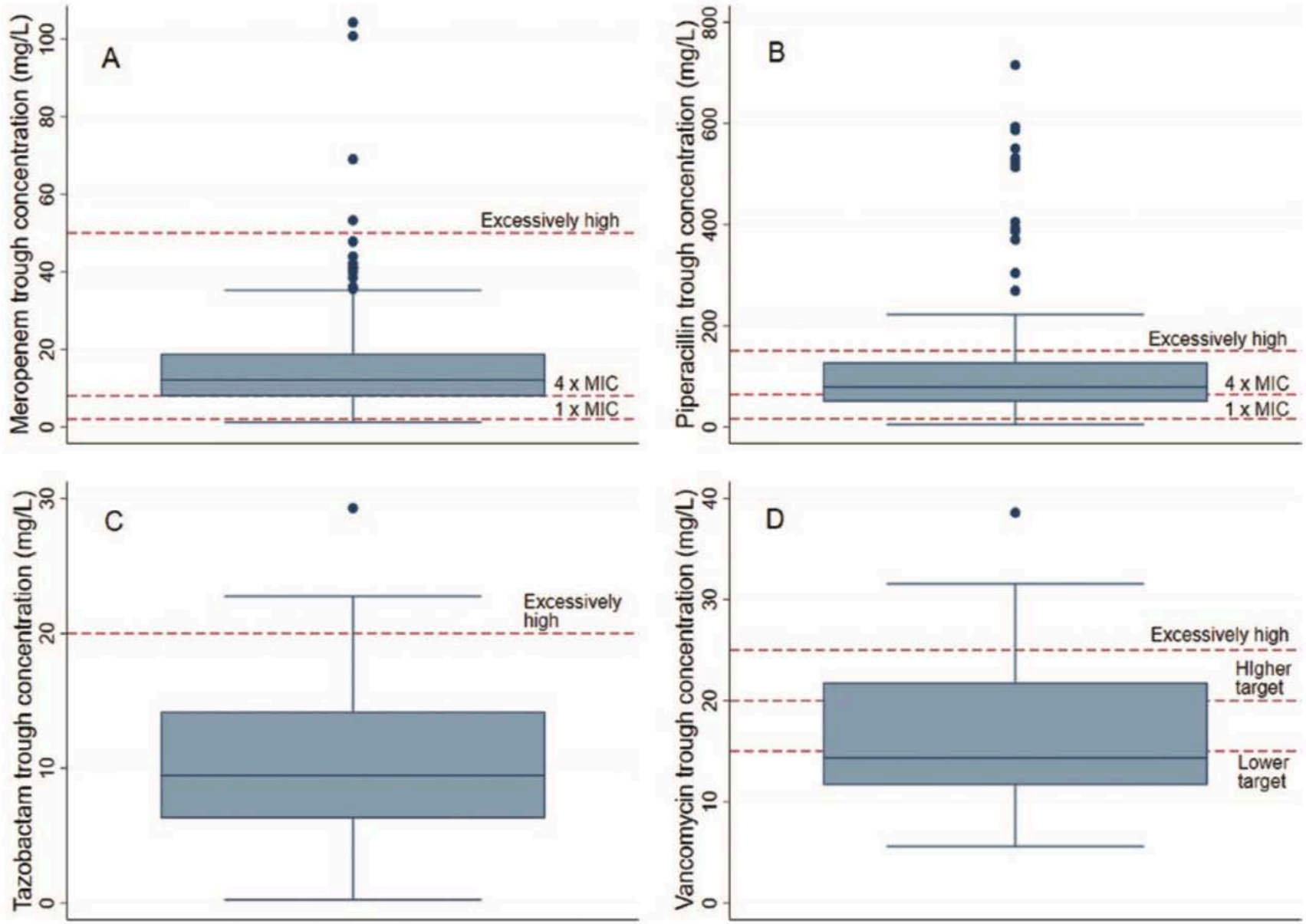


Figure 1. Patient flow diagram.

Table 3. Dose Regimens Administered to Patients at First Sampling and Their Corresponding Median (IQR) Measured Trough Concentration

Antibiotic and Dose	Cases (%)	Median (IQR), mg/L
Meropenem		
500 mg every 6 h	2 (1.0)	8.1 (2.6–NR)
500 mg every 8 h	34 (16.3)	9.0 (4.1–22.7)
500 mg every 12 h	1 (0.5)	23.9 (23.9–23.9)
1000 mg every 6 h	16 (7.7)	16.0 (14.1–24.3)
1000 mg every 8 h	117 (56.3)	11.6 (7.6–17.4)
1000 mg every 12 h	17 (8.2)	11.1 (6.6–20.6)
2000 mg every 8 h	15 (7.2)	16.2 (10.6–23.6)
2000 mg every 12 h	1 (0.5)	12.5 (12.5–12.5)
2000 mg every 24 h	1 (0.5)	13.6 (13.6–13.6)
3000 mg every 8 h	2 (1.0)	7.5 (6.1–NR)
3000 mg every 24 h	1 (0.5)	8.2 (8.2–8.2)
4000 mg every 8 h	1 (0.5)	9.0 (9.0–9.0)
Piperacillin		
1000 mg every 8 h	1 (0.6)	NR
2000 mg every 6 h	3 (1.8)	49.0 (34.5–NR)
2000 mg every 8 h	10 (6.1)	81.6 (49.9–115.7)
3000 mg every 8 h	34 (20.9)	178.7 (59.4–396.3)
3600 mg every 8 h	1 (0.6)	57.6 (57.6–57.6)
4000 mg every 6 h	34 (20.9)	121.3 (75.5–153.1)
4000 mg every 8 h	70 (42.9)	64.3 (45.0–92.9)
4000 mg every 12 h	9 (5.5)	54.3 (40.2–105.1)
4000 mg every 24 h	1 (0.6)	108.8 (108.8–108.8)
Tazobactam		
250 mg every 8 h	3 (3.0)	7.8 (4.4–NR)
375 mg every 8 h	9 (8.9)	0.6 (0.4–1.4)
500 mg every 6 h	26 (25.7)	14.7 (9.5–20.9)
500 mg every 8 h	58 (57.4)	9.4 (6.6–13.2)
500 mg every 12 h	5 (5.0)	13.3 (7.6–16.5)
Vancomycin		
750 mg every 8 h	3 (4.8)	29.3 (27.3–NR)
960 mg every 24 h	1 (1.6)	24.0 (24.0–24.0)
1000 mg every 8 h	7 (11.3)	27.1 (19.5–27.8)
1000 mg every 12 h	14 (22.6)	16.0 (12.1–23.1)
1000 mg every 24 h	26 (41.9)	12.4 (10.9–14.4)
1250 mg every 24 h	1 (1.6)	13.5 (13.5–13.5)
1500 mg every 12 h	2 (3.2)	19.6 (15.7–NR)
1500 mg every 24 h	5 (8.1)	11.8 (10.3–22.3)
2000 mg every 12 h	1 (1.6)	13.6 (13.6–13.6)
2000 mg every 24 h	2 (3.2)	12.2 (8.2–NR)

Abbreviations: IQR, interquartile range; NR, not reported.


A
Meropenem trough concentration (mg/L)
0
20
40
60
80
100
Excessively high
4 x MIC
1 x MIC
B
Piperacillin trough concentration (mg/L)
0
200
400
600
800
Excessively high
4 x MIC
1 x MIC
C
Tazobactam trough concentration (mg/L)
0
10
20
30
Excessively high
D
Vancomycin trough concentration (mg/L)
0
10
20
30
40
Excessively high
HIgher target
Lower target

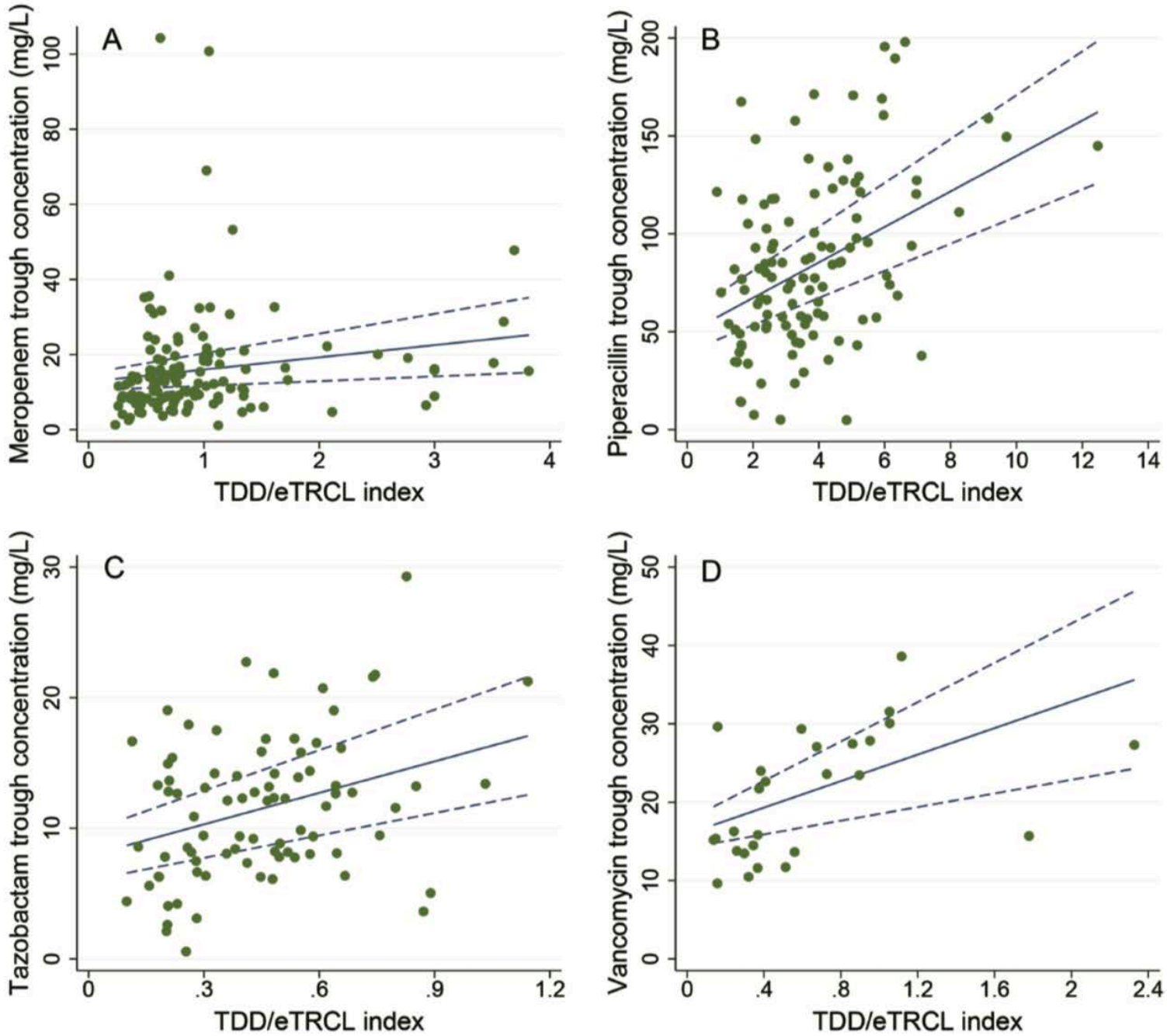

A
Meropenem trough concentration (mg/L)
0
20
40
60
80
100
0
1
2
3
4
TDD/eTRCL index
B
Piperacillin trough concentration (mg/L)
0
50
100
150
200
0
2
4
6
8
10
12
14
TDD/eTRCL index
C
Tazobactam trough concentration (mg/L)
0
10
20
30
0
.3
.6
.9
1.2
TDD/eTRCL index
D
Vancomycin trough concentration (mg/L)
0
10
20
30
40
50
0
.4
.8
1.2
1.6
2
2.4
TDD/eTRCL index

Table 5. Association Between Measured Trough Concentration and Risk of 28-Day Mortality (Unadjusted and Adjusted Hazard Ratio) by Antibiotics

Antibiotic	Mortality, n (%)	HR (95% CI)	*P*	Adjusted HR (95% CI)[a]	*P*
Meropenem (n = 187)					
2–8 mg/L	14 (34.1)	1.00		1.00	
<2 mg/L	4 (57.1)	2.02 (1.10–3.72)	.011	2.55 (1.33–4.90)	.012
>8 mg/L	71 (51.1)	1.55 (1.05–2.29)		1.39 (.89–2.15)	
Piperacillin (n = 160)					
16–64 mg/L	25 (49.0)	1.00		1.00	
<16 mg/L	3 (50.0)	1.06 (.38–2.99)	.605	1.41 (.77–2.58)[b]	.317
>64 mg/L	62 (60.2)	1.26 (.80–2.00)		1.19 (.92–1.53)[b]	
β-Lactam (n = 347)					
Meropenem or piperacillin 1× MIC–4× MIC	39 (42.4)	1.00		1.00	
Meropenem or piperacillin <1× MIC	7 (53.8)	1.41 (.73–2.76)	.212	1.54 (1.03–2.30)[b]	.053
Meropenem or piperacillin >4× MIC	133 (55.0)	1.33 (.95–1.87)		1.23 (.99–1.51)[b]	
Tazobactam (n = 101)					
≤5 mg/L	12 (63.2)	1.00		1.00	
>5 mg/L	40 (48.8)	0.66 (.39–1.13)	.127	0.74 (.58–.94)[b]	.014
Vancomycin (n = 60)					
≤15 mg/L	20 (60.6)	1.00		1.00	
>15 mg/L	9 (33.3)	0.44 (.14–1.43)	.175	0.45 (.14–1.51)	.197

For panel discussion

- Why is it important to get the discussion section right?
- Do you have any tips on writing the results and discussion?
- What strategies do you use to successfully publish research outcomes?

Next Session: September 8, 2020

Navigating a research career in the hospital sector

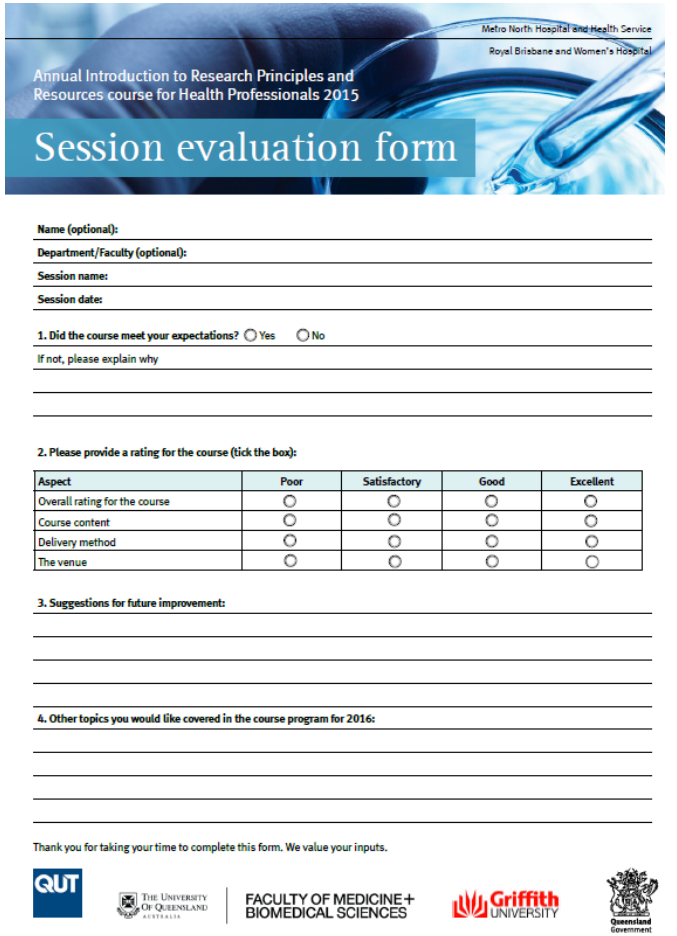
This session will showcase outcomes of nearly or recently completed higher degree researchers;
Three minute thesis format with 6 recent graduates; 20 minutes; knowledge gaps, research question, design, key outcomes, significance and impact.

Panel discussion:

- What did you learn about the process of doing research during the PhD experience?
- How well does the topic of your research align with your clinical practice?
- How are you using or would like to use your new skills and knowledge in clinical practice?

Online Feedback Form

- Please provide feedback.
- Informs scope, design and improvement in research education sessions
- We will email link to the survey for attendees
- https://metronorth.health.qld.gov.au/research/webinar-series/evaluation



Metro North Hospital and Health Service

Royal Brisbane and Women's Hospital

Annual Introduction to Research Principles and Resources course for Health Professionals 2015

Session evaluation form

Name (optional):

Department/Faculty (optional):

Session name:

Session date:

1. Did the course meet your expectations? ○ Yes ○ No

If not, please explain why

2. Please provide a rating for the course (tick the box):

Aspect	Poor	Satisfactory	Good	Excellent
Overall rating for the course	○	○	○	○
Course content	○	○	○	○
Delivery method	○	○	○	○
The venue	○	○	○	○

3. Suggestions for future improvement:

4. Other topics you would like covered in the course program for 2016:

Thank you for taking your time to complete this form. We value your inputs.

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