St George's GICU Journal Club Template

DIRECTIONS
Please answer all of the questions in the boxes provided. Wherever possible, use your own words. Cut and paste tables / illustrations or refer to specific locations within the paper concerned. Be thorough but concise. Be critical but realistic.

Reference of paper:
Please use the following format: 1st author et al. Title. Journal. Date. Volume: page range. Please also give details of any accompanying editorial.

Dimitri Karmpaliotis et al. Diagnostic and Prognostic Utility of Brain Natriuretic Peptide in Subjects Admitted to the ICU With Hypoxic Respiratory Failure Due to Noncardiogenic and Cardiogenic Pulmonary Oedema. Chest 2007:131:964-971

Introduction:
What question(s) are the authors trying to answer?

Does BNP reliably differentiate between ARDS/ALI and Cardiogenic Pulmonary Oedema (CPE).

And is the level related to outcome.

Do the authors provide a rationale to support their investigation / hypothesis?

Yes

Give a concise explanation of their rationale.

BNP has been shown to increase reliably and significantly in patients with Cardiac Failure. BNP increases when the ventricle is pressure or volume overloaded. They expected to find lower levels of BNP in patients with ARDS/ALI. They selected a group of patients in whom the diagnosis was unclear.

Is the case well presented / argued?

Yes

Consider the methods used:
What design was used – randomised control trial / controlled not randomised / cohort / case series / case report / prospective vs. retrospective / review / systematic review / consensus guideline

Prospective Study

From what population were the patients recruited – single centre (type & location) / multi-centre (types and locations) / multinational (types & locations). Given this population, how generalisable is this study?

1 surgical and 2 Medical ICUs in 2 University affiliated Hospitals. Small study, but at least 2 different institutions and medical as well as surgical patients makes more generalisable.

Describe patient numbers / important inclusion criteria / important exclusion criteria / screening & enrolment methods / number screened vs. number enrolled. Was the sample size estimated by performing a power calculation, if so, was this reasonable? Was the estimated sample size achieved? If not, why?

80 patients only. **Inclusion:** icu, acute hypoxic respiratory failure, p/f < 300 (ie sick patients!) with bilateral infiltrates on CXR. Diagnosis unclear (Decision to insert PA catheter for diagnostic purposes already made by treating clinician). Recruiting staff had to be present at time of enrolment. **Exclusion:** ACS, acute or chronic renal failure on RRT, CABG < 2 weeks previous,Previous BNP result on same admission, Known LVEF < 30%, PA cath inserted for different reason- eg haemodynamic monitoring.

80/234 PA caths in 13 month period- ? time rather than sample size target.

Briefly describe control and intervention protocols. Any good ideas? Any concerns? Where all reasonable methods used to minimise the effects of confounding variables? Did the authors measure to what extent their protocols were adhered to? Was there a clinically meaningful difference in intervention actually delivered to the 2 (or more) groups?

BNP result was well concealed from the clinicians. Confounding variables were assessed and minimised using various statistical techniques (multivariable logistic regression models, goodness of fit was assessed with Hosmer-Lemeshow test). Patients were treated at the clinicians discretion. One therefore assumes no difference in quality of treatment between the groups. Methods ensured equality as far as can be reasonably expected. One also assumes that those with suspected ALI/ARDS and those with CPE were treated differently, however there are no details on treatment.

What outcome measures were employed (primary and secondary)? How well defined were the chosen endpoints. How reliable were any measurements taken? Would alternative endpoints have been better and if so, how?

2 intensivists as “experts” decided on diagnosis after more than 10 days and the primary outcome measure was to determine any correlation between diagnosis and BNP level. Secondary outcome measure was to determine any correlation between BNP level and mortality in the different groups. Less well defined secondary outcome measures were relationship between BNP level and PCWP and BNP vs echo findings. Measurements were reliable as BNP was measured in 1 lab with an approved valid assay and haemodynamic measurements were performed by a single investigator at end expiration and the average of 3 readings was used. 74/80 patients underwent echocardiography and this was not essential to the study protocol. I think the endpoints were appropriate io the study design and protocols. Personally however I would be far more interested in a study that assesses whether BNP levels alter treatment and thereby patient

outcome to number of ventilated days, days on ICU or even morbidity/mortality.

Was the method of analysis decided upon during the design and described? Where any subgroup analyses included in the study design?

Yes, well described. Subgroups: age, gender, BMI, use of pressors, history of CHF, eGFR, Mean right atrial and PA systolic pressures.

What follow-up, if any was performed? If so duration / completeness?

Diagnosis made after at least 10 days. Followed only as far as discharge from hospital.

Consider the validity of this study

If randomised, was the method sound? Was the list concealed?

Sound method considering Prospective study. Randomisation not applicable. Well concealed (Blinded)

Where the treatment groups similar at baseline? How was this assessed? Was this assessment adequate? If not, what additional / alternative methods would have enhanced this assessment?

Strict inclusion and exclusion criteria meant groups were similar at baseline. Assessed by collection of demographics and characteristics at baseline- see table1. Similar except greater incidence of final diagnosis of CPE in the elderly, those with a past history of CHF, and those with worse kidney function.

Are all the patients enrolled in the study accounted for at conclusion?

Yes. Certainly would expect that not all eligible patients were enrolled however.

Are patients analysed in the groups to which they were randomised?

N/A

Were patients and / or clinicians blinded to treatment?

BNP only revealed after all study material gathered.

Were the groups treated similarly outside of the study intervention? Was there anything about their non-study treatment which was notable? Is there insufficient detail to draw a conclusion?

Insufficient. No details on treatment except that those that had a final diagnosis of ALI/ARDS tended to be treated with higher PEEP. It is not evident whether echo result affected treatment strategy.

Consider the reported results

Are the results well presented? Are any / all statistical analyses properly performed, reported and interpreted?

Yes. Stats seem to be properly performed and reported. Due to small study size they accepted fairly large p values for retention in the multivariate logistic regression model.

For primary outcome(s) what was the result concluded by authors? Is this justified?

BNP is helpful in differentiating between ALI/ARDS and CPE. Its greatest value is where BNP is <200 as CPE is less likely at this level. I think they do justify this to some degree. However, it is unhelpful in at least 49% of the study population (BNP 200-1200). Even at levels <200 the positive predictive value and specificity for ALI/ARDS is only 91%. It would have resulted in 8/36 patients initially thought to have CPE to have been more appropriately classified as ALI/ARDS. PCWP and echo findings (LVEF and wall motion abnormality) provided only a modest improvement in the association between BNP and ARDS.

For secondary outcome(s) was the result concluded by authors? Is this justified?

Raised BNP when adjusted for APACHE 2 score shows a strong graded relationship with mortality risk for both ALI/ARDS and CPE. Small study, p=0.03. Possibly justified. As discussed earlier the authors accepted higher p values as a consequence of the study size. A response between BNP level and outcome has been shown in a number of other studies.

What was the measured adherence to treatment protocols?

Treatment protocols assumed to have been followed- no discussion.

Where there any adverse events / effects reported?

Nil reported. Decision for PA catheter insertion was already made. Only intervention was a blood sample. I wonder what there PA catheter associated complications were and how frequently these occurred. If significant their argument for avoiding invasive methods to assist diagnosis would carry extra weight.

Consider the discussion

What were the strengths and weaknesses of this study?

Strengths: 1) Clinical diagnosis before PAC insertion 2)BNP result concealed until all other data gathered including "expert diagnosis 3) Expert review- agreed 76/80 and achieved consensus on remaining 4 patients 4) Diagnosis made using established criteria 5) Standard investigation and treatment proceeded with no incentive for different standard of care in either group 6) Single investigator collecting haemodynamic data in standard manner. **Weaknesses:** 1) Prospective study 2) Small 3) Only high risk patients. Requiring PAC for diagnosis. Associated increased mortality. (Perhaps this is the wrong group) 4) Excluded cardiac and renal patients- (in my experience this is perhaps the most diagnostically challenging group) 5) Authors used standard criteria but the diagnosis of ARDS remains challenging

Are the results compared to the literature on this topic and / or the current standard of' care?

References 17,18,22 and others. Yes. BNP can help differentiate CPE from other forms of acute respiratory failure. Its greatest value is as an exclusion at low levels especially <50. BNP<200 is a reasonable cut off. There is a suggestion that BNP increase may be an epiphenomenon of sepsis, surgery or other acute illness but there seems to be a strong correlation with impaired cardiac function. Perhaps this explains the associated increased mortality irrespective of diagnosis. To my mind this is similar to patients with a raised troponin without myocardial infarction.

Describe the authors' conclusions. Are they reasonable?

BNP in conjunction with other investigations is helpful in the evaluation of hypoxaemic patients in an ICU environment, and in particular for excluding CPE. Authors suggest that this test may in time allow a less invasive approach to diagnosis in this group of patients

What conclusions do you draw from this study?

BNP is a cheap test and easy to perform. It may be helpful in patients with respiratory failure and bilateral infiltrates on CXR when the underlying pathology is unclear.

How should this study affect our clinical practice?

Consider when diagnosis is unclear. I don't think it should affect our practice. I don't think it is particularly useful in our setting.

What should be the next steps for further study of this area?

Unless a study can show that BNP level alters treatment strategy and results in a favourable outcome for critically ill patients, I think its dubious role lies in the general medical ward. Until then for me it will remain a good, cheap and easy test looking for a good clinical indication.

One could use this as a pilot study. More centres involved, multinational with a panel of experts assessing diagnosis. I'm not convinced the PA catheter is essential to the method. As long as there is sufficient data to make an accurate diagnosis. The aim for me would be to show that we are poor at accurately assessing these patients and that BNP helps our best guess and initial treatment strategy.

Consider the references
Where all statements of fact appropriately referenced?

Yes

Did you read any of the references (please give details)? If so, did you gain any additional insights and what were they?

See "**discussion**" point 2 above(17,18,22). (17) BNP is better at predicting diagnosis of cardiac failure than LVEF on echo in this study and primary lung disorders are not associated with a rise in BNP. (1)There are more recent and better ARDS papers. 2 papers about PA caths (9) Maybe the PA cath is redundant? Showed no benefit or harm- does have complications but none fatal in this study. (10) PA cath was no more useful than a cvc in the treatment of patients with ALI in this study. PA cath caused arrhythmias. (32) Fascinating read for the Physiologists among you, but strangely enough I thought I understood by the end- how the heart copes with such awful lungs… (34) This study showed that being old and female was associated with a slightly higher BNP- I wouldn't bother reading this one but interestingly the same author produced a paper showing that patients with an increased fluid load (such as a well filled septic patient from A&E) despite a normal echo, may have an elevated BNP which drops within days. Anaesthesia and Intensive care 33(4):528-30, 2005 Aug. (37)Raised BNP is a marker of prognosis in the patient with severe sepsis.

Any additional comments / information / points for discussion.

I think the study was well thought out and the methods were sound. It would clearly have had greater power with larger numbers. I would imagine that it is hard to design a good study of a biochemical marker such as BNP. All in all I think they did well.

I found it very interesting that the initial physician got the diagnosis of CPE wrong more than 51% of the time! Is this a real problem? Are we also wrong so often? In this group of patients a BNP<200 would have excluded CPE in 8/18 (44%) wrongly assessed patients. If we really are this bad at assessing our patients then maybe BNP is more useful than I currently believe.

From my understanding BNP to some degree correlates with cardiac index. It rises in sepsis, with acute fluid loading as well as in cardiac failure. In this study the ALI/ARDS group had a median BNP of 325, well above the 200 cut off. At levels above 1200 the positive predictive value for CPE was only 75% with a specificity of 92%. It is not a diagnostic test. Its value is only in that at levels <200 CPE becomes unlikely. If one accepts that as a general principle we attempt to keep patients with ALI/ARDS dry anyway I can't see that this test adds value. In a critical care environment this test cannot replace the information gathered from continuous assessment of response to interventions and treatment. In the study echocardiography was performed in 74/80 patients. Would echo have been unnecessary if they had known the BNP result? Cardiac output monitoring (invasive or otherwise) provides ongoing assessment of a patients' response to treatment instead of just a snapshot in time. My understanding currently is that the rate of change of BNP level would make it unsuitable as a monitor of progress.

The study group was one of sick patients in whom invasive monitoring is justifiable and often a necessity. My feeling is that if BNP does have a role, it is not in the critically ill. The one instance where I think it may be useful is in the General Medical Ward or the MAU. Patients in whom one would like to avoid invasive monitoring (CVC lines etc), in a setting where echocardiography is not easily accessible AND where the diagnosis is unclear- in particular if they have other organ frailties, especially borderline renal function. (The patient not quite sick enough for ITU/HDU) My

approach has always been to treat the immediately concerning and obvious problems and monitor the response. In my experience there aren't that many patients where a reasonable initial treatment strategy can't be formulated. Having said that I have seen many people on the medical wards with deteriorating renal function on treatment for "cardiac failure". I wonder whether a low BNP level on admission might have saved their kidneys or decreased their hospital stay? I like to think that in the ICU setting however, with all our toys, that we're a little better than BNP?

I have long been a BNP cynic. This study and the other papers I read have made me revisit my thoughts. For me the difficulty is finding a truly good indication for its use.

I hope that some of you are big believers in BNP as I need some further convincing…….. I'm hoping for a little more than "its cheap, so why not".

As a side discussion, does anyone have any strong feelings about PA catheters?