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.

Canadian Critical Care Trials Group, A Randomised Trial of Diagnostic Techniques for Ventilator-Associated Pneumonia. NEJM 21/12/2006. 355;25 2619-2630

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

To see if bronchioalveolar-lavage (BAL) with quantitative culture yields superior diagnostic information when compared to endotracheal (ET) aspirate, thus allowing reduction in antibiotic use and reduced morbidity/mortality.

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

Previous studies document that reliance on ET aspiration culture frequently leads to misclassification of ventilator associated pneumonia (VAP). BAL may yield superior diagnostic information.

Give a concise explanation of their rationale.

In an observational study they found that quantitative culture of BAL fluid, as compared with culture of ET aspirate, resulted in more confident decision making, less use of antibiotics and lower mortality rates.

Is the case well presented / argued?

Yes. It is of note that previous trials have had conflicting results. They also mention the need for specialist training for BAL, thus not always making this technique available in some centres, delaying treatment.

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, multi-centre randomised trial. 2-by-2 factorial design.

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?

Patients from 28 ICUs in Canada and USA. Generalised case mix – except for immunocompromised.

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?

740 patients with suspected VAP.

Patients were stratified according to severity of illness within 24 hours of enrolment (Less severe = APACHE <24, severe = APACHE >24)

Inclusion criteria are those who received mechanical ventilation for at least 4 days if they had suspected pneumonia (new or persistent X-ray features of pneumonia without another obvious cause and any 2 of the following: temp >38^{0}C, leukocytosis (>11.0x10^3) or neutropenia (<3500/mm^3), purulent ET secretions, potentially pathogenic bacteria isolated from ET aspirate, increasing O_2 requirements.

Exclusion criteria were patients immunocompromised; considered unfit for bronchoscopy; allergic to penicillins, cephalosporins, carbapenems or ciprofloxacin; infected or colonised with pseudomonas species or MRSA; recent recipients of study drugs (ciprofloxacin within 24 hours and meropenem within 7 days before enrolment); expected to die within 72 hours after enrolment; unlikely to leave ICU within 3 weeks; pregnant or lactating; or previously enrolled in this or another interventional trial.

Power calculations suggested need for 740 patients assuming a 28 day mortality of 40%. This allowed a statistical power of 80% to detect an absolute risk reduction in 28 day mortality of 10%.

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?

They developed an implementation manual to standardise the procurement and lab processing of samples. This was sent to and agreed upon by all participating labs before study initiation.

Empirical antibiotic therapy was standardised in order to ensure any differences observed were due to diagnostic technique. Once diagnostic tests were done, patients were randomly assigned to meropenem and ciprofloxacin or meropenem alone. Antibiotics were not adjusted until sensitivities were known, at which point a single agent with narrow spectrum prescribed

according to local policy.

The ICU physician/ attending respirologist performed BAL in affected lung region, identified by CXR.

In no growth or normal flora cultures, study antibiotics were discontinued except at physician discretion in those with a high pre-test likelihood of VAP, a subjective score.

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?

Primary outcome was 28 day mortality rate.

Secondary outcome included survival in the ICU, discharge from hospital, duration of mechanical ventilation, length of ICU stay and hospital stay, response to clinical and microbiological treatment, organ-dysfunction score, and use or non-use of antibiotics after culture results were known.

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

Yes.

Study design relied upon an assumption that the 2 types of study intervention (diagnostic and antibiotic) would not interact. Confirmed by demonstration of the similarity of treatment effect between diagnostic groups.

All comparisons were controlled for APACHE score and antibiotic group.

Subgroup analysis were performed with the pre-test likelihood of VAP, severity of illness, length of stay in ICU before randomisation, prior use or non-use of antibiotics and presence or absence of high-risk organisms in the culture.

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

100% follow-up.

Consider the validity of this study

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

Treatment randomly assigned with use of central telephone system with a variable undisclosed block size

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?

Yes. No significant differences.

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

Yes

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

Yes

Were patients and / or clinicians blinded to treatment?

Yes

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?

Consider the reported results

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

Yes

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

The trial was designed to detect 10% absolute risk reduction or 25% relative risk reduction from 28 day mortality rate of 40%. The actual mortality rate was lower than expected, the study achieved a statistical power of 98% to detect absolute risk reduction of 10% but only a power of 41% to detect relative risk reduction of 40%.

The treatment effect of the 2 diagnostic tests was the same regardless of antibiotic therapy and the treatment effect of the 2 antibiotic therapies was the same regardless of the diagnostic test used.

There were no significant differences in 28 day mortality in any of the subgroup analysis.

They detected no important differences in clinical outcomes or in the use of antibiotics between the groups undergoing either diagnostic test in the main analysis or subgroup analysis.

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

There were no significant differences between the groups in time to discontinuation of mechanical ventilation, discharge from ICU or hospital.

What was the measured adherence to treatment protocols?

Where there any adverse events / effects reported?

None documented.

Consider the discussion

What were the strengths and weaknesses of this study?

Strengths: Concealed randomisation, 100% follow-up, the use of intention to treat analysis, efforts to standardise key aspects of the protocol. The large sample and multicentre nature enhance the generalisability.

Weakness: Investigators aware of study interventions and clinical judgement was involved in determining the pre-test likelihood and final classification of VAP.

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

Yes, to literature. Results consistent with 3 Spanish trials. Other trials have shown ET aspiration leads to misclassification of VAP.

Describe the authors' conclusions. Are they reasonable?

ET aspirate with non-quantitative culture to diagnose VAP is associated with clinical outcomes and antibiotic use similar to those that are associated with BAL and quantitative culture.

What conclusions do you draw from this study?

It is fine to tailor antibiotic therapy as well as make a diagnosis of VAP on the results of early ET aspirate, rather than seek a BAL, which may delay treatment, in what seemed to be the superior diagnostic tool.

How should this study affect our clinical practice?

Little really! We already send early ET aspiration samples in suspected VAP. I guess there is less urgency or need to proceed to BAL unless samples are not forthcoming. We also commence early appropriate empirical antibiotic therapy according to local policy/microbiological advice.

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

When the results of all trials are combined, there is a non-significant beneficial effect on mortality using BAL with quantitative cultures. To confirm or refute this, a randomised trial would need to include over 10000 patients per treatment group. In the setting of adequate initial empirical antibiotic use it is difficult to postulate the mechanism by which BAL with quantitative culture would increase survival.

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?

Safdar et al. Clinical and economic consequences of ventilator acquired pneumonia: a systematic review. Crit Care Med 2005;33:2184-93 Interesting paper outlining morbidity and mortality from VAP as well as its impact on costs.

Any additional comments / information / points for discussion.

Study received grants from AstraZeneca and Bayer. It is unclear why 2 empirical antibiotic groups were used in the first place other than they wished for good pseudomonas cover.