

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Development of guidance on the timeliness in response to Acute Kidney Injury Warning Stage Test Results for adults in primary care: an appropriateness ratings evaluation
AUTHORS	Blakeman, Tom; Griffith, Kathryn; Lasserson, Daniel; Lopez, Berenice; Tsang, Jung; Campbell, Stephen; Tomson, Charles

VERSION 1 - REVIEW

REVIEWER	Mark Devonald Nottingham University Hospitals NHS Trust, United Kingdom
REVIEW RETURNED	29-Jun-2016

GENERAL COMMENTS	<p>This study addresses the important subject of guideline response times to AKI e-alerts issued to primary care. AKI e-alerts were developed in various hospitals around the UK over the past few years and more recently became mandatory in all acute hospitals, with a top-down approach enforcing the use of a common KDIGO-based AKI algorithm, even where validated functional e-alerts were already operating successfully.</p> <p>The proposed mandatory extension of AKI e-alert reporting to primary care does raise concerns about how alerts will be delivered and acted upon. This study is therefore timely and has helped in the development of guidance to primary care.</p> <p>The manuscript is well written with clear objectives and sound methodology. The results are of interest but are not particularly surprising.</p> <p>I do not have any major criticisms of the study itself but I do think that the authors should discuss in more detail concerns about using a KDIGO-based AKI algorithm in primary care, when AKI in primary care remains poorly understood and where KDIGO criteria have not been validated. The authors quite rightly discuss that serum creatinine checks in primary care compared with secondary care are likely to be less frequent, have different indications and that there is a lower probability of having a reference (baseline) creatinine. Given these limitations and the results described, do the authors believe that mandatory use of AKI e-alerts in primary care is likely to be helpful or not, rather than simply stating that the study has informed the development of guidance? I wonder if they would like to nail their colours to the mast?</p>
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REVIEWER	Mark Thomas Dept of Renal Medicine Birmingham Heartlands Hospital Birmingham UK
REVIEW RETURNED	05-Jul-2016

GENERAL COMMENTS

Comments:

1. Limitations of the study are missing. The Strengths and Limitations list after the abstract does not list any limitations.
2. Introduction - whilst over 50% of AKI starts in the community, the proportion of AKI alerts being generated in primary care is much smaller, as many of the patients are actually identified in secondary care having presented there. In our experience about 10% of alerts are for patients who are not in hospital. This group of patients in primary care is nevertheless important as they include a full spectrum of disease from early AKI to end of life care. The introduction should reflect this.
3. Introduction - there is a literature on 'alert fatigue' and alert responses which should be mentioned. McCoy AB et al, AJKD 2010; 56: 832 showed that interruptive alert warnings of AKI and nephrotoxic medication use were deferred a median of four times before a definitive response. Some alert studies have found that clinician behaviour was not changed.
4. Introduction - An important study to quote here is: Automated, electronic alerts for acute kidney injury: a single-blind, parallel-group, randomised controlled trial. Wilson FP et al Lancet 2015; this showed that alerts alone did not affect outcomes.
5. Methods - not all major comorbidity groups were considered in the scenarios, where there was a partial focus on CHF. Type 2 diabetes and malignancies were not specifically considered.
6. The exact numbers of types of panelists should be given (clinical biochemistry, acute and emergency medicine and general practice). I am not sure I would want to be categorised as 'routine general practice.' Also the number of salaried, locum and GP principals should be stated.
7. Discussion - In practice there are significant differences in the care provided to AKI patients in working hours versus out of hours. The problems of OOH care are mentioned. The study did not separately ask panelists to consider scenarios that were explicitly based during OOH time. This may have not been feasible due to time / resource constraints for the panelists, but the fact that scenarios were not explicitly set during working hours or OOH needs to be mentioned, and would be an area for further research.

Also is there an example of a consensus guideline developed in this way that has been proven by later trial work?
8. Discussion - there is a new ESC guideline on HF, released in May. ESC's 2016 guidance discusses contrasting views about sudden deterioration in kidney function in HF. On the one hand it notes the link between AKI episodes and CKD. It also notes that: "increases in creatinine are not always clinically relevant, especially when they are accompanied by appropriate decongestion, diuresis and haemoconcentration." The authors should update their comment here.

Minor comments:

1. As this is a British journal I would prefer 'Medicalisation'

	Overall this is a good study which provides consensus guidelines to help primary care in managing AKI. I entirely support its publication by BMJ Open after these revisions.
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Mark Devonald

Institution and Country: Nottingham University Hospitals NHS Trust, United Kingdom

Competing Interests: None declared.

This study addresses the important subject of guideline response times to AKI e-alerts issued to primary care. AKI e-alerts were developed in various hospitals around the UK over the past few years and more recently became mandatory in all acute hospitals, with a top-down approach enforcing the use of a common KDIGO-based AKI algorithm, even where validated functional e-alerts were already operating successfully. The proposed mandatory extension of AKI e-alert reporting to primary care does raise concerns about how alerts will be delivered and acted upon. This study is therefore timely and has helped in the development of guidance to primary care. The manuscript is well written with clear objectives and sound methodology. The results are of interest but are not particularly surprising.

I do not have any major criticisms of the study itself but I do think that the authors should discuss in more detail concerns about using a KDIGO-based AKI algorithm in primary care, when AKI in primary care remains poorly understood and where KDIGO criteria have not been validated.

The following sentence has been added to the discussion on page 15:

‘Though there is evidence that AKI is associated with adverse clinical outcomes, the majority of the studies informing the development of the KDIGO classification system for AKI ‘were based on critical care databases.’⁴⁵ As such, its application may not necessarily be generalizable to the primary care setting.⁴⁵

In relation to this point, a reference has also been added to the next sentence:

‘However, irrespective of whether an AKI Warning Stage Test Result leads to confirmation of AKI or alternatively flags CKD progression, there is evidence to indicate that the e-alerts are still likely to ‘identify patients at risk of poor outcomes’ in terms of non-recovery, chronic renal replacement therapy and long-term mortality.’^{17 46}

Reference 46:

Hobbs H, Bassett P, Wheeler T, et al. Do acute elevations of serum creatinine in primary care engender an increased mortality risk? *BMC Nephrology* 2014;15(1):1-10. doi: 10.1186/1471-2369-15-206

The authors quite rightly discuss that serum creatinine checks in primary care compared with secondary care are likely to be less frequent, have different indications and that there is a lower probability of having a reference (baseline) creatinine. Given these limitations and the results described, do the authors believe that mandatory use of AKI e-alerts in primary care is likely to be helpful or not, rather than simply stating that the study has informed the development of guidance? I wonder if they would like to nail their colours to the mast?

In the Introduction (page 5), we state that ‘If implemented well, the release of AKI Warning Stage Test Results to primary care has the potential to generate major improvements in outcomes.’

In the abstract and the discussion, we state that further research is need to examine the effect of the implementation of AKI Warning Stage Test Results on health outcomes and costs. We believe this a

necessary next step.

Reviewer: 2

Reviewer Name: Mark Thomas

Institution and Country: Dept of Renal Medicine, Birmingham Heartlands Hospital, Birmingham, UK

Competing Interests: None

Comments:

1. Limitations of the study are missing. The Strengths and Limitations list after the abstract does not list any limitations.

A methodological limitation has been added to this section (see page 3). The strengths and limitations section within the discussion (page 14) has also been expanded.

2. Introduction - whilst over 50% of AKI starts in the community, the proportion of AKI alerts being generated in primary care is much smaller, as many of the patients are actually identified in secondary care having presented there. In our experience about 10% of alerts are for patients who are not in hospital. This group of patients in primary care is nevertheless important as they include a full spectrum of disease from early AKI to end of life care. The introduction should reflect this.

The introduction has been expanded (see pages 4 & 5) and now also reflects recent NICE guidance on Sepsis, which has been published since the original submission of the manuscript. Amendments include the following sentences:

'National clinical guidelines for AKI recommend 'identifying acute kidney injury in patients with acute illness' who are deemed at risk of AKI.⁶ At present, whilst a significant proportion of episodes of illness complicated by AKI start in the community, AKI tends to be identified and on hospital admission.¹⁷

'First, kidney function tests are taken in primary care for many reasons both as part of routine disease management monitoring as well as assessment of urgent care. Current data suggests that only a small proportion of all primary care serum creatinine requests generate an AKI alert.²¹ In primary care, a decision on whether or not to check kidney function needs to be tailored to the individual circumstance.⁶ Consideration needs to be given as to whether this will support clinical management. For example, blood tests are not necessary when immediate admission is required (e.g. there is evidence of sepsis).^{22 23} At the other end of the spectrum, checking kidney function tests may not be necessary for patients presenting with a minor self-limiting acute illness, such as a single episode of diarrhoea or vomiting.'

3. Introduction - there is a literature on 'alert fatigue' and alert responses which should be mentioned. McCoy AB et al, *AJKD* 2010; 56: 832 showed that interruptive alert warnings of AKI and nephrotoxic medication use were deferred a median of four times before a definitive response. Some alert studies have found that clinician behaviour was not changed.

4. Introduction - An important study to quote here is: Automated, electronic alerts for acute kidney injury: a single-blind, parallel-group, randomised controlled trial. Wilson FP et al *Lancet* 2015; this showed that alerts alone did not affect outcomes.

Revisions with supporting references have been made to the introduction to take into account points 3 and 4 (see page 5):

'Fourth, there is evidence to suggest that the introduction of 'e-alerts' in isolation are unlikely to improve health outcomes.^{24 25} In particular, 'alert fatigue' is a recognised problem limiting implementation and effectiveness.^{26 27}

5. Methods - not all major comorbidity groups were considered in the scenarios, where there was a

partial focus on CHF. Type 2 diabetes and malignancies were not specifically considered. This limitation has been acknowledged in the discussion (page 14) and as a bullet in the 'strengths and limitations' section on page 3.

6. The exact numbers of types of panelists should be given (clinical biochemistry, acute and emergency medicine and general practice). I am not sure I would want to be categorised as 'routine general practice.' Also the number of salaried, locum and GP principals should be stated. Amendments have been made to page 7 in order to provide greater clarity on the number of types of panelists including the contractual status of participating GPs. The word 'routine' has been removed from text in both the methods section and the abstract.

7. Discussion - In practice there are significant differences in the care provided to AKI patients in working hours versus out of hours. The problems of OOH care are mentioned. The study did not separately ask panelists to consider scenarios that were explicitly based during OOH time. This may have not been feasible due to time / resource constraints for the panelists, but the fact that scenarios were not explicitly set during working hours or OOH needs to be mentioned, and would be an area for further research.

The clinical scenarios considered during the consensus process were not specific to either in hours or out of hours care. Amendments have been made to the Methods section to make this more explicit (pages 6 and 7). It is now also discussed in the strengths and limitations section of the discussion on page 14:

'In addition, developing scenarios for working hours and out of hours may have produced greater clarity on timeliness in response though would have also lengthened the ratings process for panel members with the potential for 'cognitive strain.'⁴¹ On balance, the chosen response times for rating (i.e. seek immediate admission; respond within 6 hours; respond within 24 hours; respond within 72 hours) sought to evaluate appropriate actions taking into account key time frames in current clinical practice (e.g. respond within 6 hours in order to determine whether appropriate to be seen within working hours, or before next day if knowledge of test result during out of hours; respond within 72 hours to determine if appropriate to wait until Monday if knowledge of a test result on Friday afternoon/evening).'

Also is there an example of a consensus guideline developed in this way that has been proven by later trial work?

Amendments have been made to the discussion to indicate evidence of the predictive validity of quality indicators developed through the UCLA/RAND Appropriateness Method (see page 14). A further sentence has been added to make explicit that the UCLA/RAND Appropriateness Method is only the starting point and that further research is needed to provide evidence of acceptability, feasibility, reliability, sensitivity to change and predictive validity.

8. Discussion - there is a new ESC guideline on HF, released in May. ESC's 2016 guidance discusses contrasting views about sudden deterioration in kidney function in HF. On the one hand it notes the link between AKI episodes and CKD. It also notes that: "increases in creatinine are not always clinically relevant, especially when they are accompanied by appropriate decongestion, diuresis and haemoconcentration." The authors should update their comment here.

Changes have been made and the reference updated to this paragraph in the discussion (see pages 15 and 16):

'As indicated by the European Society of Cardiology Heart Failure guidelines (2016), increases in serum creatinine are not always the main clinical priority, 'especially when they are accompanied by appropriate decongestion, diuresis and haemoconcentration'⁴⁸ – although this statement was in the context of acute heart failure in hospital; data on the prognostic importance of changes in kidney function during treatment of heart failure in primary care are lacking. The ESC guidelines recommend

that 'when large increases in serum creatinine occur, care should be taken to evaluate the patient thoroughly and should include assessment of a possible renal artery stenosis, excessive hyper- or hypovolaemia, concomitant medication and hyperkalaemia, which frequently coincides with WRF (worsening renal function).'49'

Minor comments:

As this is a British journal I would prefer 'Medicalisation'

Both the term medicalization and over-diagnosis are now referred to at the relevant points in the main text and manuscript (see pages 2, 7 and 14). The term 'over-diagnosis' has been referred to as the Royal College of General Practitioners have a 'Standing Group on Overdiagnosis.' See reference 35.

Reference 35:

McCartney M, Treadwell J. The RCGP's new standing group on overdiagnosis. BMJ 2014;349 doi: 10.1136/bmj.g4454

Overall this is a good study which provides consensus guidelines to help primary care in managing AKI. I entirely support its publication by BMJ Open after these revisions.

VERSION 2 – REVIEW

REVIEWER	Mark Devonald Nottingham University Hospitals NHS Trust
REVIEW RETURNED	06-Sep-2016

GENERAL COMMENTS	The authors have addressed my questions satisfactorily, thank you.
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REVIEWER	Mark Thomas Dept of Renal Medicine Birmingham Heartlands Hospital Birmingham, UK
REVIEW RETURNED	01-Sep-2016

GENERAL COMMENTS	<p>The paper is a clearly useful addition to the literature and should be accepted. I have one quite minor optional revision which could be addressed by the authors if they wish to add to the supplementary files.</p> <p>To assist other researchers wanting to use this method in future it would be simple and helpful to add these documents to the supplementary files:</p> <ol style="list-style-type: none"> 1. The instructions document 2. The context document 3. A sample scenario - one where there was disagreement would be most useful for researchers
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