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Impact of e-Alert for Detection of Acute Kidney Injury on Processes of Care and Outcomes: Protocol for a Systematic Review and Meta-Analysis

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ABSTRACT

Introduction Acute kidney injury (AKI) is a common complication in hospitalized patients. It imposes significant risk for major morbidity and mortality. Moreover, patients suffering an episode of AKI consume considerable health resources. Recently, a number of studies have evaluated the implementation of automated electronic alerts (e-alerts) configured from electronic medical records (EMR) and clinical information systems (CIS) to warn healthcare providers of early or impending AKI in hospitalized patients. The impact of e-alerts on care processes, patient outcomes and health resource use; however, remain uncertain.

Methods and analysis We will perform a systematic review to describe and appraise e-alerts for AKI and evaluate their impact on processes of care, clinical outcomes and health services use. In consultation with a research librarian, a search strategy will be developed and electronic databases (i.e., Medline, Embase, CINAHL, Cochrane Library and Inspec via Engineering Village) searched. Selected grey literature sources will also be searched. Search themes will focus on e-alerts and AKI. Citation screening, selection, quality assessment and data abstraction will be performed in duplicate. The primary analysis will be narrative; however, where feasible, pooled analysis will be performed. Each e-alert will be described according to trigger, type of alert, target recipient and degree of intrusiveness. Pooled effect estimates will be described, where applicable.

Ethics and dissemination Our systematic review will synthesize the literature on the value of e-alerts to detect AKI, to impact care processes, patient-centered outcomes and resource use, and also identify key knowledge gaps and barriers to implementation. This is a fundamental step in a broader research programme aimed to understand the ideal structure of e-alerts, target population and methods for implementation to derive benefit. Research ethics approval is not required for this review.

Trial registration number International Prospective Register for Systematic Reviews (PROSPERO) number CRD42016033033.

BACKGROUND

Acute kidney injury (AKI) is an increasingly encountered complication, affecting 13-18% of hospitalized patients[1] and up to 60% of those admitted to an intensive care unit (ICU)[2 3]. Importantly, AKI has a significant modifying impact on patient outcome, imposing an increased risk for major morbidity, including chronic kidney disease (CKD), accelerated progression to end-stage kidney disease (ESKD), and mortality. Prior observational data have shown even relatively small increases in serum creatinine of 27 μmol/L (0.3 mg/dl) have been associated with several fold increased risk of mortality[1]. Moreover, patients suffering an episode of AKI consume greater resources and incur higher costs, largely from intensified monitoring, investigations, and support necessitating longer hospital stays.

Consensus statements by expert panels currently recommend early tailored investigations and management measures for AKI such as urinalysis, ultrasound, drug dose adjustment and avoidance of nephrotoxins[4 5]. The impact of these recommendations, which are mostly focused on harm avoidance, remains to be clear determined. One of the challenges on evaluating the impact of these and other process of care measures (i.e., monitoring, investigations, interventions) is the early recognition of AKI by clinicians. For example, Wilson et al. showed that more than 25% of patients whose creatinine doubled had no documentation of AKI in their medical record[6].

In 1994, Rind et al. proposed a software algorithm that automatically tracked creatinine changes and once a threshold was reached, sent an alert through the hospital mailbox to the responsible team. However, this alert process did not integrate clinical decision support or specific recommendations related to further monitoring, investigations or treatments[7]. Since this publication, a number of studies using various designs of "alerts", some automated and some relying on human interactions,

have been described [8]. In AKI, e-alerts are generally triggered by changes in serum creatinine and/or urinary output. Studies have evaluated the impact of these alerts on either care process (i.e., enhanced monitoring, added testing, modification or discontinuation of potential nephrotoxic drugs, etc.) or patient-related clinical outcomes (i.e.. worsening AKI, receipt of RRT, mortality, etc.). However, studies to date have shown inconsistent findings, with some showing improved outcomes[9-11] and others describing no differences[12 13]. Moreover, wide variation in the methodology processes for e-alerting have been described in the literature, such as criteria and thresholds for triggering activation, the format of the alert, the target recipient of the alert and the degree of intrusiveness.

These observations would imply the relative benefits for developing and implementing an e-alert system, along with its idealized structure for the detection of AKI and its impact on patient care processes, outcomes and health resource use remain uncertain. Indeed, the Acute Dialysis Quality Initiative (ADQI) recently convened a consensus meetings focused on big data applications for AKI[14], including the need for continued development, refinement and rigorous evaluation of e-alerting in AKI[15 16]. Accordingly, we propose to conduct an evidence synthesis and meta-analysis to describe the various e-alerts systems for AKI detection and to assess their impact for patient care, outcomes and resource use.

OBJECTIVES

The aims of our systematic review are to:

1. Describe the definitions and methods utilized for designing and implementing an electronic alert (i.e., automated, partially automated, target audience, intrusiveness) for AKI.

2. Determine the impact of electronic alerting for AKI on quality of care indicators and processes of care (i.e., changes in frequency of monitoring, investigations [including urinalysis and ultrasound] and management [including medication review, chart documentation of AKI, decrease in the use of nephrotoxins, drugs dosage adjustment, fluid prescription, vasopressors or diuretics use, time to action and ICU or nephrology consult]).
3. Determine the impact of electronic alerting for AKI on patient-centered clinical outcomes (i.e., peak creatinine, progression of AKI, proportion of patients fulfilling criteria for KDIGO stage 3 or RIFLE stage F, receipt of renal replacement therapy [RRT], kidney recovery and mortality).
4. Determine the impact of electronic alerting for AKI on health services use (i.e., ICU admission, ICU readmission, ICU length of stay, hospital length of stay).

METHODS

Study Design

A systematic review will be performed to characterize e-alerts for AKI and assess their impact on processes of care, clinical outcomes and health services use, using the guidelines from The Cochrane Collaboration and Center for Reviews and Dissemination and described according to the PRISMA-P guideline (available at: http://www.systematicreviewsjournal.com/content/4/1/1)[17].

Study Registration

The systematic review is registered at PROSPERO (www.crd.york.ac.uk/prospero). Registration number CRD42016033033.

Criteria for considering studies for this review

Inclusion criteria:

1. *Design*: original data from randomized or quazi-randomized trials, observational cohort studies or before and after studies.

2. *Study population*: all hospitalized patients (i.e., pediatric or adult) admitted to an ICU or a ward (i.e., exclude ED and outpatient settings).

3. *Intervention*: Studies that implement an e-alert (i.e., automated or partially automated) for the detection and diagnosis of AKI, using a clearly defined operational definition (i.e., RIFLE, AKIN, KDIGO, other etc.)

4. *Outcomes*: Studies that report the impact of AKI e-alerts on at least one process of care indicator, patient-centered outcome or measure of health resource utilization.

Exclusion criteria:

Studies will be excluded that do not fulfill all of the above criteria; published in a language other than English or French or use non-electronic alert.

Search methods for identification of studies

PROSPERO (http://www.crd.york.ac.uk/prospero) was searched for any registered systematic reviews on this topic (October 9th 2015).

The search strategy will be developed in consultation with a research librarian at the Alberta Research Centre for Health Evidence (ARCHE) at the University of Alberta. The search strategy will undergo further peer-review by a second research librarian using the Peer Review of Electronic Search Strategies checklist[18]. A comprehensive search for Acute Kidney Injury (AKI) and electronic

alerts (e-alerts) concepts will be conducted in bibliographic databases: Ovid Medline, Ovid Embase, CINAHL, Cochrane Library, and Inspec. We will also search grey literature sources for health technology assessments and technical reports. Websites for e-alert technology producers (e.g., Epic, Philips, iMDsoft, Cerner) will be searched in addition to the conference proceedings from the *American Society of Nephrology, Society of Critical care Medicine, International Symposium on Intensive Care and Emergency Medicine, European Society of Intensive Care Medicine, and American Medical Informatics Association (AMIA)*. Concept searches for AKI will use a modified version of a published search filter[19], and database searches will be limited to publications from 1990 to current in English and French. Appropriate truncation and wildcards will be used in the search to account for plurals and/or variations in the spelling of search terms. Bibliographic records will be exported to an EndNote X7 (Thomson Reuters, Philadelphia, Pennsylvania) database for screening. The cited and citing references of selected key studies will also be searched for relevant articles. See appendix A for the proposed Ovid Medline strategy.

Study Selection

Potentially eligible articles will be initially identified by having two authors independently review the titles and abstracts of all articles identified by the search. The full text of all articles deemed potentially relevant will be retrieved and two authors will independently review the full text for inclusion using pre-defined eligibility criteria. Any disagreements that arise will be resolved through discussion or referral to a third party.

Data extraction

Data will be abstracted from relevant studies using a standardized electronic data collection form (Appendix 2). This form will undergo pilot testing. This abstraction will be performed in duplicate

by the same two authors. Any disagreements that arise will be resolved through discussion or referral to a third party. The authors of the retrieved studies and/or documents will be contacted for further information as necessary. Study methodological quality will be rated using the using the Modified Downs and Black checklist (Appendix 3)[20].

Analysis

The primary analysis will be mixed narrative and meta-analytic where feasible. Each alert will be described according to trigger, type of alert, recipient and degree of intrusiveness (either passive, active, disruptive or very disruptive). We adapted our intrusiveness scale from a tool developed by Partners and Health Care for drug-drug interactions and published by Paterno et al.[21]. All authors reached consensus on use of the modified version (see Appendix 4 for details). When possible, pooled effect estimates of the impact of e-alerts on selected processes of care, patient-centered outcomes and resource use will be reported. We will assess and quantify statistical heterogeneity for each pooled summary estimate using Cochran's Q statistic and the I^2 statistic, respectively[22]. Pooled analysis will be performed using random effects models and reported as odds ratios with 95% confidence intervals for categorical variables and weighted mean differences 95% confidence intervals for continuous variables, respectively. Meta-regression analysis will be performed to assess for possible sources of heterogeneity according to the following pre-defined variables: criteria use for AKI definition (KDIGO, RIFLE, AKIN), type of unit (mixed ward/ICU vs. ward alone), study design (observational vs. RCT vs. before and after) and degree of intrusiveness of the alert (passive vs. active vs. disruptive/very disruptive). Publication bias will be assessed using Egger's regression model, and visualized with a funnel plot[23]. All analyses will be performed using STATA statistical software, version 14 (Stata Corp, College Station, Texas).

EXPECTED LIMITATIONS

Some limitations are to be expected. First, based on previous preliminary search of the literature, we expect most of the studies to be included in our systematic review will have before and after design, have moderate quality, and show heterogeneity in treatment effect contingent on the process or outcome measured. Moreover, as the context in which an e-alert is introduced may affect its effectiveness and the context may vary across studies, we expect this parameter to increase heterogeneity between the selected studies. Accordingly, we may not be able to draw firm conclusions with a high level of confidence on the efficacy and effectiveness of e-alerts in AKI. Importantly, we anticipate the majority of studies to have short-term follow-up for patient-centered outcomes.

CONCLUSION

In conclusion, this systematic review aims to critically appraise the scope of e-alerts developed for the detection and classification of AKI, along with define the ideal type and format of e-alert for AKI. We recognize there may be context-specific e-alert methods more suitable for selected circumstances. Importantly, we aim to define the most robust and important care processes, patient outcomes, and resource use indicators that should be integrated and measured when developing and implementing an e-alert system and/or performing future clinical investigations or quality assurance audits. Finally, we aim to synthesize the available evidence on the impact of AKI e-alerts on these same processes of care, patient-centered and health resources utilization outcomes.

Contributorship: PL and SMB draft the manuscript; RF created the research strategy; PMV, NMS, FWP and OR reviewed the manuscript and provided their comment

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Impact of e-Alert for Detection of Acute Kidney Injury on Processes of Care and Outcomes: Protocol for a Systematic Review and Meta-Analysis (Appendix)

1

Appendix 1. Example of the search strategy for Medline

1. exp Acidosis/ci
2. exp Acute Kidney Injury/
3. (Blood Urea Nitrogen/ or Reperfusion Injury/ or (cardiogenic adj1 shock*).tw,kf. or (critical* adj (care or ill* or patient*)).mp. or icu.tw,kf. or intensive care.mp. or (isch?emi* adj (reperfusion or injur*)).tw,kf. or life-threatening.mp. or ((multi* organ or multiorgan) adj (failure or dys-function or dysfunction)).mp. or poly-angiitis.mp. or polyangiitis.mp. or poly-arteritis.mp. or polyarteritis.mp. or rhabdo-myolysis.mp. or rhabdomyolysis.mp. or sepsis.mp. or septic.mp. or thrombo-cytopeni*.tw,kf. or thrombocytopeni*.tw,kf. or tubular cell*.tw,kf. or vasculit*.mp. or wegener* granulomatosis.mp.) and ((creatinin$ or de-hydrat* or dehydrat* or dialysis or kidney or renal).mp. or ur?emi*.tw,kf.)
4. *Hemolytic-Uremic Syndrome/
5. *Hemorrhagic Fever with Renal Syndrome/
6. Kidney Cortex Necrosis/
7. exp Kidney Diseases/ci
8. (Kidney Diseases/ or glomerular filtration rate*.tw,kf. or isch?emi* reperfusion injur*.tw,kf. or (renal adj (dys-function* or dysfunction* or failure or function or impairment or insufficienc*)).mp.) and (Acute Disease/ or Cardiovascular Diseases/ or exp *Cardiovascular Surgical Procedures/ or exp *Cardiovascular System/su or *Contrast Media/ or exp *Diagnostic Imaging/ or Ischemia/ or exp Neurologic Manifestations/ or exp Substance-Related Disorders/ or ci.fs. or cardiac surg*.mp. or cardio-pulmonary*.tw,kf. or cardiopulmonary.tw,kf. or cirrhosis.ti. or micro angiopath*.tw,kf. or microangiopath*.tw,kf. or pre operative*.tw,kf. or preoperative*.tw,kf. or post operative*.tw,kf. or postoperative*.tw,kf. or revers*.tw,kf.)
9. Nephritis, Interstitial/
10. Renal Insufficiency/
11. (acute adj2 (kidney or renal or nephr* or glomer* or h?emodialy* or dialysis)).mp.
12. aki.tw,kf.
13. anti gbm.tw,kf.
14. anuri*.mp.
15. (anti glomerular or antiglomerular).mp.
16. azot?emi*.mp.
17. (glomerulonephritis.mp. or nephrit*.tw,kf.) and ((acute or anca*).tw,kf. or crescentic.mp. or rapidly progressive.tw,kf.)
18. h?emolytic ur?emi*.tw,kf.
19. hepatorenal syndrome.mp.
20. ((impair* or improved or recover*) adj2 renal function).tw,kf.
21. (induced adj (kidney or renal)).tw,kf.
22. ((interstitial or tubulointerstitial) adj nephr*).tw,kf.
23. (injur* or isch?emi* or reperfusion or contrast medi*).mp. and (renal tubul* or tubular).tw,kf.
24. ((kidney or renal) adj failure*).tw,kf.
25. ((kidney or renal) adj injur*).tw,kf.
26. ((kidney or renal) adj insufficienc*).tw,kf.
27. ((kidney* or renal) adj isch?emi*).tw,kf.
28. (nephropath* and (cast or (contrast* adj (agent* or induced or medi*)) or crystal* or iodinated or radiocontrast*)).mp.
29. nephrotox*.tw,kf.
30. (obstruct* adj2 (kidney* or nephropath* or renal or uropathy)).tw,kf.
31. oliguri*.mp.
32. (pre renal or prerenal).tw,kf.
33. (renal adj (hypo perfusion or hypoperfusion)).tw,kf.
34. (renal adj2 thrombosis).tw,kf.
35. (thrombotic adj (thrombocytopeni* or microangiopathy)).tw,kf.
36. (tubul* adj (damage* or injur* or necrosis)).tw,kf.
37. (worsening and renal).tw,kf.
38. or/1-37 [Combined AKI MeSH & textwords - modified filter from Hildebrand 2014 doi:10.1093/ndt/gft531]
39. Automation/
40. Automation, Laboratory/

41. Biological Markers/ and (alarm* or alert* or information system* or messag* or notif* or remind* or reporting system* or warn*).tw,kf.
42. Biomedical Technology/
43. exp Cell Phones/
44. Clinical Alarms/
45. Clinical Laboratory Information Systems/
46. Creatinine/bl and (alarm* or alert* or information system* or messag* or notif* or remind* or reporting system* or warn*).tw,kf.
47. Decision Support Systems, Clinical/
48. Drug Therapy, Computer-Assisted/
49. exp Electronic Health Records/
50. Health Information Systems/
51. Hospital Information Systems/
52. Information Systems/
53. Management Information Systems/
54. Medical Informatics/
55. Medical Informatics Applications/
56. Medical Order Entry Systems/
57. Medical Records Systems, Computerized/
58. Medication Systems, Hospital/
59. Monitoring, Physiologic/is
60. Point-of-Care Systems/
61. Reminder Systems/
62. Software/ and (alarm* or alert* or information system* or messag* or notif* or remind* or reporting system* or warn*).tw,kf.
63. User-Computer Interface/
64. ((acute kidney injury network* or AKIN or AKI network*) and (alarm* or alert* or information system* or messag* or notif* or remind* or reporting system* or warn*)).tw,kf.
65. (alarm* and (automat* or comput* or digit* or e mail or electronic or email or software or sms or text*)).tw,kf.
66. (alert* and (automat* or comput* or digit* or e mail or electronic or email or software or system* or sms or text*)).tw,kf.
67. ((app or application* or apps or phon* or smart phon* or smartphon* or telephon*) and (alert* or messag* or notif* or remind* or warn*)).tw,kf.
68. automated system*.tw,kf.
69. ((bed side or bedside or electronic) adj2 system*).tw,kf.
70. computer assist*.tw,kf.
71. (comput* adj2 system*).tw,kf.
72. computeri?ed decision support*.tw,kf.
73. (computeri?ed adj2 order entr*).tw,kf.
74. CPOE*.tw,kf.
75. delta check*.tw,kf.
76. (e alarm* or e alert* or e notification* or e report* or e warning*).tw,kf.
77. electronic order entry system*.tw,kf.
78. (electronic adj2 (recogni* or report*)).tw,kf.
79. information system*.tw,kf.
80. (integrated adj2 system*).tw,kf.
81. ((KDIGO or kidney disease improving global outcomes) and (alarm* or alert* or information system* or messag* or notif* or remind* or reporting system* or warn*)).tw,kf.
82. (laborator* adj2 alert*).tw,kf.
83. (messag* and (automat* or comput* or digit* or e mail or electronic or email or software or system* or sms or text*)).tw,kf.
84. (monitoring adj2 (automat* or comput* or digit* or electronic or software or system*)).tw,kf.
85. (notif* adj2 (automat* or comput* or digit* or e mail or electronic or email or software or system* or sms or text*)).tw,kf.
86. pathology software.tw,kf.
87. (real time adj (alert* or notification*)).tw,kf.

88. (reminder* adj2 (automat* or comput* or digit* or e mail or electronic or email or software or sms or system* or text*)).tw,kf.
89. ((RIFLE or risk injury failure loss) and (alarm* or alert* or information system* or messag* or notif* or remind* or reporting system* or warn*)).tw,kf.
90. (serum creatinine and (alarm* or alert* or information system* or messag* or notif* or remind* or reporting system* or warn*)).tw,kf.
91. surveillance system*.tw,kf.
92. (urinary output* and (alarm* or alert* or information system* or messag* or notif* or remind* or reporting system* or warn*)).tw,kf.
93. (warn* adj2 (automat* or comput* or digit* or e mail or electronic or email or software or sms or text*)).tw,kf.
94. or/39-93 [Combined MeSH & textwords for e-alerts]
95. and/38,94 [Combined searches for AKI & e-alerts]
96. limit 95 to (english or french) [Language limit]
97. limit 96 to yr="1990-current" [Publication date limit]
98. remove duplicates from 97

Appendix 2. Data to be collected in the form

Data	Description
Author	First author name
References	Journal, Issue, volume, pages
Impact factor	Impact factor of the journal in the year published
Country	Country in which the study was conducted
Year	Start and end date of study
Design	
Type	RCT, quasi-RCT, before and after, observational [if observational what is the control group]
Blinding	Is the study blinded and to who
Allocation concealment	For RCT is the allocation concealment preserved
Number of centers	Single-center, multi-center
Setting	Ward, ICU, both
Inclusion criteria	List all inclusion criteria of the study
Exclusion criteria	List all exclusion criteria of the study
Study Quality	See Appendix 2
Funding	Industry vs. publicly funded vs. both
Type of alert	
Threshold for activation	Criteria used to diagnose AKI (RIFLE, KDIGO, etc.)
What is the baseline creatinine used?	Definition of baseline creatinine
How is a baseline creatinine value determined when none is available	Method by which a baseline creatinine is defined when none is available
Timing	Instantaneous or batched alerts (frequency if batched)

Appendix 2. Data to be collected in the form (continued)

Data	Description
Type of alert (continued)	
Target provider of alert	Physician/resident/associate/MRP/pharmacy/multiple
Training given to the caring team [i.e. any formation about AKI (diagnosis, investigations, management) given before the study by the research team to clinicians (attendings, residents, fellows, pharmacists or nurse practitioners) who will receive the alert	Yes or no
Method of communication	
Alert sent to the recipient	e-mail, page, call, text
Alert in patient's EMR	Notification (text), red flag
Mechanism of alert generation	
Where is it detected?	EMR, dedicated alerting system, biochemistry LIMS
Automation	Automated or semi-automated
What is generated	Message or call or both
Degree of intrusiveness	See Appendix 4
Content	
Integrated clinical decision support	YES/NO
If integrated clinical decision support, *how* is it integrated?	Integrated in the message of the alert or alert provide a link (to recommendation) or verbal opinion by member of the search team
If integrated clinical decision support, *what* is included?	

Appendix 2. Data to be collected in the form (continued)

Data	Description
Content (continued)	
Diagnostic	Urinalysis, ultrasound
Monitoring	Repeat creatinine [if provided, when], u/o measurement
If integrated clinical decision support, *what* is included? (continued)	
Mechanism of harm avoidance	medication list review, nephrotoxins to avoid [including contrast], drugs dose adjustment, direct a consult with a specialist [either nephrology or ICU]
Degree of intelligence of clinical decision support	Is the clinical decision support generic (ex. Click here to order a urinalysis) or context specific (ex. The patient is taking gentamicin click here to d/c the medication)
If AKI progress is there another alert generated	Yes or no
Outcomes measured in the study	
Process outcomes	
Time to drugs adjustment	Yes or no
Chart documentation of AKI	Yes or no
Medication list revision	Yes or no
Patients who received a nephrotoxins	Yes or no
ICU or nephrology consult	Yes or no
Follow-up creatinine	Yes or no

Appendix 2. Data to be collected in the form (continued)

Data	Description
Outcomes measured in the study (continued)	
Any investigation (ultrasound or urinalysis)	Yes or no
Use of fluid, diuretics or vasopressor	Yes or no
Patient-centered outcomes	
Receipt of RRT	Yes or no
Creatinine [peak creatinine, % progression creatinine, % patients whose creatinine progress, % patients who progress to stage 3 AKI by KDIGO or stage F by RIFLE, recovery]	Yes or no
Death [either ICU, 7-day, hospital, 30 days, long-term [however defined]	Yes or no
Health resources use	
ICU admission	Yes or no
ICU readmission	Yes or no
ICU length of stay	Yes or no
Hospital length of stay	Yes or no
Results	
Patients related data	
Number	Total number of patients included
Age (mean [SD])	

Appendix 2. Data to be collected in the form (continued)

Data	Description
Results (continued)	
% male	
CKD status	As percentage
Baseline creatinine	In umol/L
Enrolment creatinine	In umol/L
Diagnostic	Medical/surgical/cardiac surgical
Process outcomes [as stated above]	All value related to process outcomes entered separately to be analyze in meta-analysis
Clinical outcomes [as stated above]	All value related to clinical outcomes entered separately to be analyze in meta-analysis
Health services use [as stated above]	All value related to health services use entered separately to be analyze in meta-analysis

Appendix 3: Study Quality Assessment - Modified Downs and Black Score (14)

Criteria	Score
Reporting	
Is the hypothesis/aim/objective of the study clearly described?	No = 0 ; Yes = 1
Are the main outcomes to be measured clearly described in the Introduction or Methods section?	No = 0 ; Yes = 1
Are the characteristics of the patients included in the study clearly described?	No = 0 ; Yes = 1
Are the main findings of the study clearly described?	No = 0 ; Yes = 1
Does the study provide estimates of the random variability in the data for the main outcomes?	No = 0 ; Yes = 1
Have all important adverse events that may be a consequence of the intervention been reported?	No = 0 ; Yes = 1
Have the characteristics of patients lost to follow-up been described?	No = 0 ; Yes = 1
Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	No = 0 ; Yes = 1
External validity	
Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	No = 0 ; Yes = 1
Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	No = 0 ; Yes = 1
Internal validity – bias	
If any of the results of the study were based on "data dredging", was this made clear?	No = 0 ; Yes = 1
In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients.	No = 0 ; Yes = 1
Were the statistical tests used to assess the main outcomes appropriate?	No = 0 ; Yes = 1
Was compliance with the intervention/s reliable?	No = 0 ; Yes = 1
Were the main outcome measures used accurate (valid and reliable)?	No = 0 ; Yes = 1
Internal validity - confounding	
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	No = 0 ; Yes = 1
Were losses of patients to follow-up taken into account?	No = 0 ; Yes = 1
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	No = 0 ; Yes = 1
Disclosure	
Was funding disclosed?	No = 0 ; Yes = 1

Overall Quality
13-19 = good
7 – 12 = moderate
<7 = poor

Appendix 4. Degree of intrusiveness gradation system

Grade	Level of Disruptiveness	Description	Generic Example
1	Passive	An alert is generated and displayed in the EMR/CIS. This alert does not disrupt provider workflow or require acknowledgement.	A patient fulfills criteria for KDIGO AKI stage 2 in the EMR/CIS. The following alert is generated and displayed: *AKI stage 2*
2	Active	An alert is generated and displayed in the EMR/CIS or a phone call is given to the attending physician. This alert is disruptive. This could be in the form of a specific alert [pop-up] window or flashing alert within the EMR/CIS. This alert could also generate a page, mobile text and/or email of the alert or can be a verbal notification from the lab to the most responsible provider (MRP). When electronic, this alert does not require acknowledgement. When it is a phone call, no repeat call is scheduled	A patient fulfills criteria for KDIGO AKI stage 2 in the EMR/CIS. In addition to the passive alert, the following alert is generated and sent to the MRPs pager, mobile, and/or email: *Patient XX has developed AKI stage 2*
3	Disruptive	An alert is generated and displayed in the EMR/CIS. This alert has a higher level of disruptiveness. This could be in the form of a specific alert [pop-up] window or flashing alert within the EMR/CIS and will generate a page, mobile text and/or email to notify the most responsible provider (MRP) of the alert. This alert will requires acknowledgement in the EMR/CIS. Serial repeat pages, mobile texts and/or emails alerts are generated at fixed times until the alert is acknowledged in the EMR/CIS. The alert may also not disappeared until a positive action (ex. completing a care bundle) has been undertaken.	A patient fulfills criteria for KDIGO AKI stage 2 in the EMR/CIS. In addition to the passive/active alert, the following alert is generated and sent to the MRPs pager, mobile, and/or email: *Patient XX has developed AKI stage 2. To avoid additional alerts, this must be confirmed in the patient's EMR.*

129

Appendix 4. Degree of intrusiveness gradation system (continued)

Grade	Level of Disruptiveness	Description	Generic Example
4	Very disruptive	An alert is generated and displayed in the EMR/CIS. This alert has the highest level of disruptiveness to workflow. This alert would have similar form to the above alerts; and will directly disrupt EMR/CIS activities, require acknowledgement and specific actions prior disarming.	A patient fulfills criteria for KDIGO AKI stage 2 in the EMR/CIS. In addition to the passive/active alert, the following alert is generated and sent to the MRPs pager, mobile, and/or email: *Patient XX has developed AKI stage 2.* *Proposed [action] cannot be performed because [AKI risk modification].* *Clinical Decision Support: do not [administer nephrotoxin] due to risk of worsening AKI; consult nephrology.*

BMJ Open

Impact of e-Alert for Detection of Acute Kidney Injury on Processes of Care and Outcomes: Protocol for a Systematic Review and Meta-Analysis

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Keywords:	electronic alerts, computerized decision support, acute kidney injury

Impact of e-Alert for Detection of Acute Kidney Injury on Processes of Care and Outcomes: Protocol for a Systematic Review and Meta-Analysis

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ABSTRACT

Introduction Acute kidney injury (AKI) is a common complication in hospitalized patients. It imposes significant risk for major morbidity and mortality. Moreover, patients suffering an episode of AKI consume considerable health resources. Recently, a number of studies have evaluated the implementation of automated electronic alerts (e-alerts) configured from electronic medical records (EMR) and clinical information systems (CIS) to warn healthcare providers of early or impending AKI in hospitalized patients. The impact of e-alerts on care processes, patient outcomes and health resource use; however, remain uncertain.

Methods and analysis We will perform a systematic review to describe and appraise e-alerts for AKI and evaluate their impact on processes of care, clinical outcomes and health services use. In consultation with a research librarian, a search strategy will be developed and electronic databases (i.e., Medline, Embase, CINAHL, Cochrane Library and Inspec via Engineering Village) searched. Selected grey literature sources will also be searched. Search themes will focus on e-alerts and AKI. Citation screening, selection, quality assessment and data abstraction will be performed in duplicate. The primary analysis will be narrative; however, where feasible, pooled analysis will be performed. Each e-alert will be described according to trigger, type of alert, target recipient and degree of intrusiveness. Pooled effect estimates will be described, where applicable.

Ethics and dissemination Our systematic review will synthesize the literature on the value of e-alerts to detect AKI, to impact care processes, patient-centered outcomes and resource use, and also identify key knowledge gaps and barriers to implementation. This is a fundamental step in a broader research programme aimed to understand the ideal structure of e-alerts, target population and methods for implementation to derive benefit. Research ethics approval is not required for this review.

Trial registration number International Prospective Register for Systematic Reviews (PROSPERO) number CRD42016033033.

BACKGROUND

Acute kidney injury (AKI) is an increasingly encountered complication, affecting 13-18% of hospitalized patients[1] and up to 60% of those admitted to an intensive care unit (ICU)[2 3]. Importantly, AKI has a significant modifying impact on patient outcome, imposing an increased risk for major morbidity, including chronic kidney disease (CKD), accelerated progression to end-stage kidney disease (ESKD), and mortality. Prior observational data have shown even relatively small increases in serum creatinine of 27 μmol/L (0.3 mg/dl) have been associated with several fold increased risk of mortality[1]. Moreover, patients suffering an episode of AKI consume greater resources and incur higher costs, largely from intensified monitoring, investigations, and support necessitating longer hospital stays.

Consensus statements by expert panels currently recommend early tailored investigations and management measures for AKI such as urinalysis, ultrasound, drug dose adjustment and avoidance of nephrotoxins[4 5]. The impact of these recommendations, which are mostly focused on harm avoidance, remains to be clear determined. One of the challenges on evaluating the impact of these and other process of care measures (i.e., monitoring, investigations, interventions) is the early recognition of AKI by clinicians. For example, Wilson et al. showed that more than 25% of patients whose creatinine doubled had no documentation of AKI in their medical record[6].

In 1994, Rind et al. proposed a software algorithm that automatically tracked creatinine changes and once a threshold was reached, sent an alert through the hospital mailbox to the responsible team. However, this alert process did not integrate clinical decision support or specific recommendations related to further monitoring, investigations or treatments[7]. Since this publication, a number of studies using various designs of "alerts", some automated and some relying on human interactions,

have been described [8]. In AKI, e-alerts are generally triggered by changes in serum creatinine and/or urinary output. Studies have evaluated the impact of these alerts on either care process (i.e., enhanced monitoring, added testing, modification or discontinuation of potential nephrotoxic drugs, etc.) or patient-related clinical outcomes (i.e.. worsening AKI, receipt of RRT, mortality, etc.). However, studies to date have shown inconsistent findings, with some showing improved outcomes[9-11] and others describing no differences[12 13]. Moreover, wide variation in the methodology processes for e-alerting have been described in the literature, such as criteria and thresholds for triggering activation, the format of the alert, the target recipient of the alert and the degree of intrusiveness.

These observations would imply the relative benefits for developing and implementing an e-alert system, along with its idealized structure for the detection of AKI and its impact on patient care processes, outcomes and health resource use remain uncertain. Indeed, the Acute Dialysis Quality Initiative (ADQI) recently convened a consensus meetings focused on big data applications for AKI[14], including the need for continued development, refinement and rigorous evaluation of e-alerting in AKI[15 16]. Accordingly, we propose to conduct an evidence synthesis and meta-analysis to describe the various e-alerts systems for AKI detection and to assess their impact for patient care, outcomes and resource use.

OBJECTIVES

The aims of our systematic review are to:

1. Describe the definitions and methods utilized for designing and implementing an electronic alert (i.e., automated, partially automated, target audience, intrusiveness) for AKI.

2. Determine in hospitalized adult patients the impact of electronic alerting for AKI compared to no alerting on quality of care indicators and processes of care (i.e., changes in frequency of monitoring, investigations [including urinalysis and ultrasound] and management [including medication review, chart documentation of AKI, decrease in the use of nephrotoxins, drugs dosage adjustment, fluid prescription, vasopressors or diuretics use, time to action and ICU or nephrology consult]).
3. Determine in hospitalized adult patients the impact of electronic alerting for AKI compared to no alerting on patient-centered clinical outcomes (i.e., peak creatinine, progression of AKI, proportion of patients fulfilling criteria for KDIGO stage 3 or RIFLE stage F, receipt of renal replacement therapy [RRT], kidney recovery and mortality).
4. Determine in hospitalized adult patients the impact of electronic alerting for AKI compared to no alerting on health services use (i.e., ICU admission, ICU readmission, ICU length of stay, hospital length of stay).

METHODS

Study Design

A systematic review will be performed to characterize e-alerts for AKI and assess their impact on processes of care, clinical outcomes and health services use, using the guidelines from The Cochrane Collaboration and Center for Reviews and Dissemination and described according to the PRISMA-P guideline (available at: http://www.systematicreviewsjournal.com/content/4/1/1) (Appendix 1).

Study Registration

The systematic review is registered at PROSPERO (www.crd.york.ac.uk/prospero). Registration number CRD42016033033.

Criteria for considering studies for this review

Inclusion criteria:

1. *Design*: original data from randomized or quasi-randomized trials, observational cohort studies or before and after studies.

2. *Population*: all hospitalized patients (i.e., pediatric or adult) admitted to an ICU or a ward (i.e., exclude ED and outpatient settings).

3. *Intervention*: Studies that implement an e-alert (i.e., automated or partially automated) for the detection and diagnosis of AKI, using a clearly defined operational definition (i.e., RIFLE, AKIN, KDIGO, other etc.)

4. *Outcomes*: Studies that report the impact of AKI e-alerts on at least one process of care indicator, patient-centered outcome or measure of health resource utilization.

Exclusion criteria:

Studies will be excluded that do not fulfill all of the above criteria; published in a language other than English or French or use non-electronic alert.

Search methods for identification of studies

PROSPERO (http://www.crd.york.ac.uk/prospero) was searched for any registered systematic reviews on this topic (October 9th 2015).

The search strategy will be developed in consultation with a research librarian at the Alberta Research Centre for Health Evidence (ARCHE) at the University of Alberta. The search strategy will undergo further peer-review by a second research librarian using the Peer Review of Electronic Search Strategies checklist[17]. A comprehensive search for Acute Kidney Injury (AKI) and electronic alerts (e-alerts) concepts will be conducted in bibliographic databases: Ovid Medline, Ovid Embase, CINAHL, Cochrane Library, and Inspec. We will also search grey literature sources for health technology assessments and technical reports. Websites for e-alert technology producers (e.g., Epic, Philips, iMDsoft, Cerner) will be searched in addition to the conference proceedings from the *American Society of Nephrology, Society of Critical care Medicine, International Symposium on Intensive Care and Emergency Medicine, European Society of Intensive Care Medicine, and American Medical Informatics Association (AMIA)*. Concept searches for AKI will use a modified version of a published search filter[18], and database searches will be limited to publications from 1990 to current in English and French. Appropriate truncation and wildcards will be used in the search to account for plurals and/or variations in the spelling of search terms. Bibliographic records will be exported to an EndNote X7 (Thomson Reuters, Philadelphia, Pennsylvania) database for screening. The cited and citing references of selected key studies will also be searched for relevant articles. See appendix 2 for the proposed Ovid Medline strategy.

Study Selection

Potentially eligible articles will be initially identified by having two authors independently review the titles and abstracts of all articles identified by the search. The full text of all articles deemed potentially relevant will be retrieved and two authors will independently review the full text for inclusion using pre-defined eligibility criteria. Any disagreements that arise will be resolved through discussion or referral to a third party.

Data extraction

Data will be abstracted from relevant studies using a standardized electronic data collection form (Appendix 3). This form will undergo pilot testing. This abstraction will be performed in duplicate by the same two authors. Any disagreements that arise will be resolved through discussion or referral to a third party. The authors of the retrieved studies and/or documents will be contacted for further information as necessary. Study methodological quality will be rated using the using the Modified Downs and Black checklist (Appendix 4)[19].

Outcomes

1. Primary patient-centered outcome will be all-cause mortality as primarily determined by each study. Secondary outcomes will be ICU mortality, 28/30-day mortality, hospital mortality, peak creatinine, progression of AKI, proportion of patients fulfilling criteria for KDIGO stage 3 or RIFLE stage F, receipt of renal replacement therapy [RRT], and kidney recovery.

2. Primary outcome for health-service use will be hospital length of stay. Secondary outcomes will be ICU admission, ICU length of stay, and ICU readmission.

3. Primary outcome for processes of care indicators will be dose-adjustment and/or discontinuation of nephrotoxins. Secondary outcomes will be changes in frequency of monitoring, investigations [including urinalysis and ultrasound] and management [including medication review, chart documentation of AKI, fluid prescription, vasopressors or diuretics use, time to action and ICU or nephrology consult].

Analysis

The primary analysis will be mixed narrative and meta-analytic where feasible. Each alert will be described according to trigger, type of alert, recipient and degree of intrusiveness (either passive, active, disruptive or very disruptive). We adapted our intrusiveness scale from a tool developed by Partners and Health Care for drug-drug interactions and published by Paterno et al.[20]. All authors reached consensus on use of the modified version (Appendix 5 for details). When feasible, data will be summarized and pooled to generate effect estimates of the impact of e-alerts on selected patient-centered outcomes, health resource use and processes of care. We will assess and quantify statistical heterogeneity for each pooled summary estimate using Cochran's Q statistic and the I^2 statistic, respectively[21]. Pooled analysis will be performed using random effects models and reported as odds ratios with 95% confidence intervals for categorical variables and weighted mean differences 95% confidence intervals for continuous variables, respectively. Sub-group analysis for categorical variables or meta-regression for continuous variables will be performed to assess for possible sources of heterogeneity according to the following pre-defined variables: criteria use for AKI definition (KDIGO, RIFLE, AKIN), type of unit (mixed ward/ICU vs. ward alone), study design (observational vs. RCT vs. before and after), study quality (good vs moderate vs poor [see Appendix 4 for definitions]) and degree of intrusiveness of the alert (passive vs. active vs. disruptive/very disruptive). Publication bias will be assessed using Egger's regression model, and visualized with a funnel plot[22]. Finally, the strength of the body of evidence will be assessed using the GRADE evidence system (http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665072.html). All analyses will be performed using STATA statistical software, version 14 (Stata Corp, College Station, Texas).

EXPECTED LIMITATIONS

Some limitations are to be expected. First, based on previous preliminary search of the literature, we expect most of the studies to be included in our systematic review will have before and after design, have moderate quality, and show heterogeneity in treatment effect contingent on the process or outcome measured. Moreover, as the context in which an e-alert is introduced may affect its effectiveness and the context may vary across studies, we expect this parameter to increase heterogeneity between the selected studies. Accordingly, we may not be able to draw firm conclusions with a high level of confidence on the efficacy and effectiveness of e-alerts in AKI. Importantly, we anticipate the majority of studies to have short-term follow-up for patient-centered outcomes.

CONCLUSION

In conclusion, this systematic review aims to critically appraise the scope of e-alerts developed for the detection and classification of AKI, along with define the ideal type and format of e-alert for AKI. We recognize there may be context-specific e-alert methods more suitable for selected circumstances. Importantly, we aim to define the most robust and important care processes, patient outcomes, and resource use indicators that should be integrated and measured when developing and implementing an e-alert system and/or performing future clinical investigations or quality assurance audits. Finally, we aim to synthesize the available evidence on the impact of AKI e-alerts on these same processes of care, patient-centered and health resources utilization outcomes.

ETHICS AND DISSEMINATION

Our systematic review will synthesize the literature on the value of e-alerts to detect AKI, to impact care processes, patient-centered outcomes and resource use, and also identify key knowledge gaps

and barriers to implementation. This is a fundamental step in a broader research programme aimed to understand the ideal structure of e-alerts, target populations and methods for implementation to derive benefit. Research ethics approval is not required for this review. The results will be presented in national as well as international relevant conferences in poster or oral presentations. The final manuscript will be published in a peer-reviewed journal.

Author contributions: SMB conceived the study. PL and SMB draft the manuscript; RF created the research strategy; PMV, NMS, FWP and OR reviewed the manuscript and provided their comment. SMB is the guarantor of the review.

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Impact of e-Alert for Detection of Acute Kidney Injury on Processes of Care and Outcomes: Protocol for a Systematic Review and Meta-Analysis (Appendix)

Appendix 1. PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review **See page 1, line 2**
Update	1b	If the protocol is for an update of a previous systematic review, identify as such **NOT APPLICABLE**
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number **See page 6, lines 136-137**
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author **See page 1, lines 5-21**
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review **See page 11, line 259-261**
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments **NOT APPLICABLE**
Support:		
Sources	5a	Indicate sources of financial or other support for the review **See page 11, line 266**
Sponsor	5b	Provide name for the review funder and/or sponsor **See page 11, line 266**
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol **See page 11, line 266**
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known **See pages 3-4, lines 65-106**

Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) **See pages 4-5, lines 108-124**
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review **See page 6, lines 139-152 and page 7, line 169**
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage **See pages 6-7, lines 154- 174**
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated **See Appendix 1**
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review **See page 7, line 171**
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) **See page 7, lines 176-181**
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators **See page 8, lines 184-189**
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications. **See Appendix 2**
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale **See page 8, lines 191-202**
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis **See page 8, lines 188-189**

Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised **See page 9, lines 212-213**
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ) **See page 9, lines 213-215**
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) **See pages 9, lines 217-223**
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned **See page 9, lines 207-211**
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) **See page 9, lines 223-224**
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) **See page 9, lines 224-225**

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Appendix 2. Example of the search strategy for Medline

1. exp Acidosis/ci
2. exp Acute Kidney Injury/
3. (Blood Urea Nitrogen/ or Reperfusion Injury/ or (cardiogenic adj1 shock*).tw,kf. or (critical* adj (care or ill* or patient*)).mp. or icu.tw,kf. or intensive care.mp. or (isch?emi* adj (reperfusion or injur*)).tw,kf. or life-threatening.mp. or ((multi* organ or multiorgan) adj (failure or dys-function or dysfunction)).mp. or poly-angiitis.mp. or polyangiitis.mp. or poly-arteritis.mp. or polyarteritis.mp. or rhabdo-myolysis.mp. or rhabdomyolysis.mp. or sepsis.mp. or septic.mp. or thrombo-cytopeni*.tw,kf. or thrombocytopeni*.tw,kf. or tubular cell*.tw,kf. or vasculit*.mp. or wegener* granulomatosis.mp.) and ((creatinin$ or de-hydrat* or dehydrat* or dialysis or kidney or renal).mp. or ur?emi*.tw,kf.)
4. *Hemolytic-Uremic Syndrome/
5. *Hemorrhagic Fever with Renal Syndrome/
6. Kidney Cortex Necrosis/
7. exp Kidney Diseases/ci
8. (Kidney Diseases/ or glomerular filtration rate*.tw,kf. or isch?emi* reperfusion injur*.tw,kf. or (renal adj (dys-function* or dysfunction* or failure or function or impairment or insufficienc*)).mp.) and (Acute Disease/ or Cardiovascular Diseases/ or exp *Cardiovascular Surgical Procedures/ or exp *Cardiovascular System/su or *Contrast Media/ or exp *Diagnostic Imaging/ or Ischemia/ or exp Neurologic Manifestations/ or exp Substance-Related Disorders/ or ci.fs. or cardiac surg*.mp. or cardio-pulmonary*.tw,kf. or cardiopulmonary.tw,kf. or cirrhosis.ti. or micro angiopath*.tw,kf. or microangiopath*.tw,kf. or pre operative*.tw,kf. or preoperative*.tw,kf. or post operative*.tw,kf. or postoperative*.tw,kf. or revers*.tw,kf.)
9. Nephritis, Interstitial/
10. Renal Insufficiency/
11. (acute adj2 (kidney or renal or nephr* or glomer* or h?emodialy* or dialysis)).mp.
12. aki.tw,kf.
13. anti gbm.tw,kf.
14. anuri*.mp.
15. (anti glomerular or antiglomerular).mp.
16. azot?emi*.mp.
17. (glomerulonephritis.mp. or nephrit*.tw,kf.) and ((acute or anca*).tw,kf. or crescentic.mp. or rapidly progressive.tw,kf.)
18. h?emolytic ur?emi*.tw,kf.
19. hepatorenal syndrome.mp.
20. ((impair* or improved or recover*) adj2 renal function).tw,kf.
21. (induced adj (kidney or renal)).tw,kf.
22. ((interstitial or tubulointerstitial) adj nephr*).tw,kf.
23. (injur* or isch?emi* or reperfusion or contrast medi*).mp. and (renal tubul* or tubular).tw,kf.
24. ((kidney or renal) adj failure*).tw,kf.
25. ((kidney or renal) adj injur*).tw,kf.
26. ((kidney or renal) adj insufficienc*).tw,kf.
27. ((kidney* or renal) adj isch?emi*).tw,kf.
28. (nephropath* and (cast or (contrast* adj (agent* or induced or medi*)) or crystal* or iodinated or radiocontrast*)).mp.
29. nephrotox*.tw,kf.
30. (obstruct* adj2 (kidney* or nephropath* or renal or uropathy)).tw,kf.
31. oliguri*.mp.
32. (pre renal or prerenal).tw,kf.
33. (renal adj (hypo perfusion or hypoperfusion)).tw,kf.
34. (renal adj2 thrombosis).tw,kf.
35. (thrombotic adj (thrombocytopeni* or microangiopathy)).tw,kf.
36. (tubul* adj (damage* or injur* or necrosis)).tw,kf.
37. (worsening and renal).tw,kf.
38. or/1-37 [Combined AKI MeSH & textwords - modified filter from Hildebrand 2014 doi:10.1093/ndt/gft531]
39. Automation/
40. Automation, Laboratory/

41. Biological Markers/ and (alarm* or alert* or information system* or messag* or notif* or remind* or reporting system* or warn*).tw,kf.
42. Biomedical Technology/
43. exp Cell Phones/
44. Clinical Alarms/
45. Clinical Laboratory Information Systems/
46. Creatinine/bl and (alarm* or alert* or information system* or messag* or notif* or remind* or reporting system* or warn*).tw,kf.
47. Decision Support Systems, Clinical/
48. Drug Therapy, Computer-Assisted/
49. exp Electronic Health Records/
50. Health Information Systems/
51. Hospital Information Systems/
52. Information Systems/
53. Management Information Systems/
54. Medical Informatics/
55. Medical Informatics Applications/
56. Medical Order Entry Systems/
57. Medical Records Systems, Computerized/
58. Medication Systems, Hospital/
59. Monitoring, Physiologic/is
60. Point-of-Care Systems/
61. Reminder Systems/
62. Software/ and (alarm* or alert* or information system* or messag* or notif* or remind* or reporting system* or warn*).tw,kf.
63. User-Computer Interface/
64. ((acute kidney injury network* or AKIN or AKI network*) and (alarm* or alert* or information system* or messag* or notif* or remind* or reporting system* or warn*)).tw,kf.
65. (alarm* and (automat* or comput* or digit* or e mail or electronic or email or software or sms or text*)).tw,kf.
66. (alert* and (automat* or comput* or digit* or e mail or electronic or email or software or system* or sms or text*)).tw,kf.
67. ((app or application* or apps or phon* or smart phon* or smartphon* or telephon*) and (alert* or messag* or notif* or remind* or warn*)).tw,kf.
68. automated system*.tw,kf.
69. ((bed side or bedside or electronic) adj2 system*).tw,kf.
70. computer assist*.tw,kf.
71. (comput* adj2 system*).tw,kf.
72. computeri?ed decision support*.tw,kf.
73. (computeri?ed adj2 order entr*).tw,kf.
74. CPOE*.tw,kf.
75. delta check*.tw,kf.
76. (e alarm* or e alert* or e notification* or e report* or e warning*).tw,kf.
77. electronic order entry system*.tw,kf.
78. (electronic adj2 (recogni* or report*)).tw,kf.
79. information system*.tw,kf.
80. (integrated adj2 system*).tw,kf.
81. ((KDIGO or kidney disease improving global outcomes) and (alarm* or alert* or information system* or messag* or notif* or remind* or reporting system* or warn*)).tw,kf.
82. (laborator* adj2 alert*).tw,kf.
83. (messag* and (automat* or comput* or digit* or e mail or electronic or email or software or system* or sms or text*)).tw,kf.
84. (monitoring adj2 (automat* or comput* or digit* or electronic or software or system*)).tw,kf.
85. (notif* adj2 (automat* or comput* or digit* or e mail or electronic or email or software or system* or sms or text*)).tw,kf.
86. pathology software.tw,kf.
87. (real time adj (alert* or notification*)).tw,kf.

88. (reminder* adj2 (automat* or comput* or digit* or e mail or electronic or email or software or sms or system* or text*)).tw,kf.
89. ((RIFLE or risk injury failure loss) and (alarm* or alert* or information system* or messag* or notif* or remind* or reporting system* or warn*)).tw,kf.
90. (serum creatinine and (alarm* or alert* or information system* or messag* or notif* or remind* or reporting system* or warn*)).tw,kf.
91. surveillance system*.tw,kf.
92. (urinary output* and (alarm* or alert* or information system* or messag* or notif* or remind* or reporting system* or warn*)).tw,kf.
93. (warn* adj2 (automat* or comput* or digit* or e mail or electronic or email or software or sms or text*)).tw,kf.
94. or/39-93 [Combined MeSH & textwords for e-alerts]
95. and/38,94 [Combined searches for AKI & e-alerts]
96. limit 95 to (english or french) [Language limit]
97. limit 96 to yr="1990-current" [Publication date limit]
98. remove duplicates from 97

Appendix 3. Proposed data variable for extraction.

Data	Description
Author	First author name
References	Journal, Issue, volume, pages
Impact factor	Impact factor of the journal in the year published
Country	Country in which the study was conducted
Year	Start and end date of study
Design	
Type	RCT, quasi-RCT, before and after, observational [if observational what is the control group]
Blinding	Is the study blinded and to who
Allocation concealment	For RCT is the allocation concealment preserved
Number of centers	Single-center, multi-center
Setting	Ward, ICU, both
Inclusion criteria	List all inclusion criteria of the study
Exclusion criteria	List all exclusion criteria of the study
Study Quality	See Appendix 2
Funding	Industry vs. publicly funded vs. both
Type of alert	
Threshold for activation	Criteria used to diagnose AKI (RIFLE, KDIGO, etc.)
What is the baseline creatinine used?	Definition of baseline creatinine
How is a baseline creatinine value determined when none is available	Method by which a baseline creatinine is defined when none is available
Timing	Instantaneous or batched alerts (frequency if batched)

Appendix 3. Data to be collected in the form (continued)

Data	Description
Type of alert (continued)	
Target provider of alert	Physician/resident/associate/MRP/pharmacy/multiple
Training given to the caring team [i.e. any formation about AKI (diagnosis, investigations, management) given before the study by the research team to clinicians (attendings, residents, fellows, pharmacists or nurse practitioners) who will receive the alert	Yes or no
Method of communication	
Alert sent to the recipient	e-mail, page, call, text
Alert in patient's EMR	Notification (text), red flag
Mechanism of alert generation	
Where is it detected?	EMR, dedicated alerting system, biochemistry LIMS
Automation	Automated or semi-automated
What is generated	Message or call or both
Degree of intrusiveness	See Appendix 4
Content	
Integrated clinical decision support	Yes or no
If integrated clinical decision support, *how* is it integrated?	Integrated in the message of the alert or alert provide a link (to recommendation) or verbal opinion by member of the search team
If integrated clinical decision support, *what* is included?	

Appendix 3. Data to be collected in the form (continued)

Data	Description
Content (continued)	
Diagnostic	Urinalysis, ultrasound
Monitoring	Repeat creatinine [if provided, when], u/o measurement
If integrated clinical decision support, *what* is included? (continued)	
Mechanism of harm avoidance	medication list review, nephrotoxins to avoid [including contrast], drugs dose adjustment, direct a consult with a specialist [either nephrology or ICU]
Degree of intelligence of clinical decision support	Is the clinical decision support generic (ex. Click here to order a urinalysis) or context specific (ex. The patient is taking gentamicin click here to d/c the medication)
If AKI progress is there another alert generated	Yes or no
Outcomes measured in the study	
Process outcomes	
Time to drugs adjustment	Yes or no
Chart documentation of AKI	Yes or no
Medication list revision	Yes or no
Patients who received a nephrotoxins	Yes or no
ICU or nephrology consult	Yes or no
Follow-up creatinine	Yes or no

Appendix 3. Data to be collected in the form (continued)

Data	Description
Outcomes measured in the study (continued)	
Any investigation (ultrasound or urinalysis)	Yes or no
Use of fluid, diuretics or vasopressor	Yes or no
Patient-centered outcomes	
Receipt of RRT	Yes or no
Creatinine [peak creatinine, % progression creatinine, % patients whose creatinine progress, % patients who progress to stage 3 AKI by KDIGO or stage F by RIFLE, recovery]	Yes or no
Death [either ICU, 7-day, hospital, 30 days, long-term [however defined]	Yes or no
Health resources use	
ICU admission	Yes or no
ICU readmission	Yes or no
ICU length of stay	Yes or no
Hospital length of stay	Yes or no
Results	
Patients related data	
Number	Total number of patients included
Age (mean [SD])	

Appendix 3. Data to be collected in the form (continued)

Data	Description
Results (continued)	
% male	
CKD status	As percentage
Baseline creatinine	In umol/L
Enrolment creatinine	In umol/L
Diagnostic	Medical/surgical/cardiac surgical
Process outcomes [as stated above]	All value related to process outcomes entered separately to be analyze in meta-analysis
Clinical outcomes [as stated above]	All value related to clinical outcomes entered separately to be analyze in meta-analysis
Health services use [as stated above]	All value related to health services use entered separately to be analyze in meta-analysis

Appendix 4: Study Quality Assessment - Modified Downs and Black Score (14)

Criteria	Score
Reporting	
Is the hypothesis/aim/objective of the study clearly described?	No = 0 ; Yes = 1
Are the main outcomes to be measured clearly described in the Introduction or Methods section?	No = 0 ; Yes = 1
Are the characteristics of the patients included in the study clearly described?	No = 0 ; Yes = 1
Are the main findings of the study clearly described?	No = 0 ; Yes = 1
Does the study provide estimates of the random variability in the data for the main outcomes?	No = 0 ; Yes = 1
Have all important adverse events that may be a consequence of the intervention been reported?	No = 0 ; Yes = 1
Have the characteristics of patients lost to follow-up been described?	No = 0 ; Yes = 1
Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	No = 0 ; Yes = 1
External validity	
Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	No = 0 ; Yes = 1
Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	No = 0 ; Yes = 1
Internal validity – bias	
If any of the results of the study were based on "data dredging", was this made clear?	No = 0 ; Yes = 1
In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients?	No = 0 ; Yes = 1
Were the statistical tests used to assess the main outcomes appropriate?	No = 0 ; Yes = 1
Was compliance with the intervention/s reliable?	No = 0 ; Yes = 1
Were the main outcome measures used accurate (valid and reliable)?	No = 0 ; Yes = 1
Internal validity - confounding	
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	No = 0 ; Yes = 1
Were losses of patients to follow-up taken into account?	No = 0 ; Yes = 1
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	No = 0 ; Yes = 1
Disclosure	
Was funding disclosed?	No = 0 ; Yes = 1

Overall Quality
13-19 = good
7 – 12 = moderate
<7 = poor

Appendix 5. Degree of intrusiveness gradation system

Grade	Level of Disruptiveness	Description	Generic Example
1	Passive	An alert is generated and displayed in the EMR/CIS. This alert does not disrupt provider workflow or require acknowledgement.	A patient fulfills criteria for KDIGO AKI stage 2 in the EMR/CIS. The following alert is generated and displayed: *AKI stage 2*
2	Active	An alert is generated and displayed in the EMR/CIS or a phone call is given to the attending physician. This alert is disruptive. This could be in the form of a specific alert [pop-up] window or flashing alert within the EMR/CIS. This alert could also generate a page, mobile text and/or email of the alert or can be a verbal notification from the lab to the most responsible provider (MRP). When electronic, this alert does not require acknowledgement. When it is a phone call, no repeat call is scheduled	A patient fulfills criteria for KDIGO AKI stage 2 in the EMR/CIS. In addition to the passive alert, the following alert is generated and sent to the MRPs pager, mobile, and/or email: *Patient XX has developed AKI stage 2*
3	Disruptive	An alert is generated and displayed in the EMR/CIS. This alert has a higher level of disruptiveness. This could be in the form of a specific alert [pop-up] window or flashing alert within the EMR/CIS and will generate a page, mobile text and/or email to notify the most responsible provider (MRP) of the alert. This alert will requires acknowledgement in the EMR/CIS. Serial repeat pages, mobile texts and/or emails alerts are generated at fixed times until the alert is acknowledged in the EMR/CIS. The alert may also not disappeared until a positive action (ex. completing a care bundle) has been undertaken.	A patient fulfills criteria for KDIGO AKI stage 2 in the EMR/CIS. In addition to the passive/active alert, the following alert is generated and sent to the MRPs pager, mobile, and/or email: *Patient XX has developed AKI stage 2. To avoid additional alerts, this must be confirmed in the patient's EMR.*

Appendix 5. Degree of intrusiveness gradation system (continued)

Grade	Level of Disruptiveness	Description	Generic Example
4	Very disruptive	An alert is generated and displayed in the EMR/CIS. This alert has the highest level of disruptiveness to workflow. This alert would have similar form to the above alerts; and will directly disrupt EMR/CIS activities, require acknowledgement and specific actions prior disarming.	A patient fulfills criteria for KDIGO AKI stage 2 in the EMR/CIS. In addition to the passive/active alert, the following alert is generated and sent to the MRPs pager, mobile, and/or email: *Patient XX has developed AKI stage 2.* *Proposed [action] cannot be performed because [AKI risk modification].* *Clinical Decision Support: do not [administer nephrotoxin] due to risk of worsening AKI; consult nephrology.*