Impact of selective digestive decontamination on respiratory tract *Candida* among patients with suspected ventilator associated pneumonia. A meta-analysis.

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Abstract:

Purpose: to establish the incidence of respiratory tract colonization with *Candida* (RT *Candida*) among ICU patients receiving mechanical ventilation within studies in the literature. Also of interest is its relationship with candidemia and the relative importance of topical antibiotic (TA) use as within studies of selective digestive decontamination (SDD) versus other candidate risk factors towards it.

Methods: The incidence of RT *Candida* was extracted from component (control and intervention) groups decanted from studies of various TA and non-TA ICU infection prevention methods and summary estimates derived using random effects. A benchmark RT *Candida* incidence to provide overarching calibration was derived using (observational) groups from studies without any prevention method under study. A multi-level regression model of group level data was undertaken using generalized estimating equation (GEE) methods.

Results: RT *Candida* data were sourced from 113 studies. The benchmark RT *Candida* incidence is 1·3; 0·9 -1.8% (mean and 95% confidence intervals). Membership of a concurrent control group of a study of SDD ($p=0.02$), the group wide presence of candidemia risk factors ($p<0.001$) and proportion of trauma admissions ($p=0.004$) but neither the year of study publication, nor membership of any other component group, nor the mode of respiratory sampling are predictive of the RT *Candida* incidence. RT *Candida* and candidemia incidences are correlated.

Conclusions: RT *Candida* incidence can serve as a basis for benchmarking. Several relationships have been identified. The increased incidence among concurrent control groups of SDD studies cannot be appreciated in any single study examined in isolation.

Key words: Intensive care unit; Topical antibiotic; Selective Digestive Decontamination; Ventilator associated pneumonia; *Candida*.

Introduction

Respiratory tract colonization with *Candida* (RT *Candida*) among patients with suspected ventilator associated pneumonia (VAP) has been reported in numerous studies [1-113]. Both the overall incidence and the clinical significance for the individual patient are uncertain. True *Candida* pneumonia in this patient group is thought to be rare [114, 115]. Among a tally of 2490 isolates from 24 studies, fungi (species unspecified) accounted for only 0.9% of pathogenic isolates [116]. While current guidelines [114, 115] do not recommend treatment of RT *Candida*, it remains of interest for at least four reasons.

Firstly, colonization with *Candida* is believed to be a key intermediary step towards invasive candidiasis although the role of RT *Candida* in this respect is unclear. The respiratory tract, being a site not normally colonized by *Candida*, may provide a unique insight into factors influencing the incidence of *Candida* colonization. Thirdly, RT *Candida* may be a risk factor for specific bacterial infections due to molecular interactions [117, 118].

Finally, the influence topical antibiotic (TA) use as a method to prevent ICU acquired bacterial colonization and infection, as within studies of selective digestive decontamination (SDD) and selective oro-pharyngeal decontamination (SOD) [119, 120], on the incidence of *Candida* colonization is of longstanding interest. This question was raised in the first study of SDD [74, 142]. There appear to be subtle contextual effects of using topical antibiotics in the ICU on the incidence of candidemia [121], as with bacteremia [122] and also as with Ventilator Associated Pneumonia [123], which are

evident only through benchmarking the control group rates of these studies and which are not seen in studies of non-TA methods of ICU infection prevention.

RT *Candida* data is available from numerous studies of a broad range of VAP prevention methods [119, 120, 124-135]. Among this evidence base are those with concurrent versus non-concurrent study designs together with other study designs including those without any intervention. This heterogeneous evidence base provides a natural experiment [136, 137] with which to address some of these questions at the group level using methods as used in the analysis of cluster randomized trials.

Materials and methods,

Study selection and decant of groups

The literature search and analytic approach used here is as described previously [121]. These seven steps (Fig. 1; numbered arrows) are as follows;

1. An electronic search of PubMed, The Cochrane database and Google Scholar for systematic reviews containing potentially eligible studies was undertaken using the following search terms; “ventilator associated pneumonia”, “mechanical ventilation”, “intensive care unit”, each combined with either “meta-analysis” or “systematic review” up to December 2013.
2. Systematic reviews of studies of patient populations requiring prolonged (> 24 hours) ICU admission were then streamed into one of three categories; systematic reviews containing studies in which there was no intervention, studies with SDD as the intervention, or studies with an intervention other than SDD, for the prevention of VAP. For the purpose of this study, SDD is defined here as the use of protocolized topical antibiotic prophylaxis applied by the gastric or oro-pharyngeal route in the intervention group with or without the additional use of a parenteral antibiotic or any anti-fungal agent.
3. The studies were screened against the following eligibility criteria. Inclusion criteria; incidence data for ventilator associated pneumonia extractable as an incidence proportion being expressed as a proportion of numbers of patients among patients with an ICU stay of at least 24 hours. Exclusion criteria; studies limited to patients with the acute respiratory distress syndrome. Studies in a language other than English were included when the required data had been abstracted in an English language systematic review.

4. A hand search was undertaken for additional studies not identified within systematic reviews but otherwise meeting the eligibility criteria.
5. All eligible studies were then collated and any duplicate studies were removed.
6. Groups of patients receiving mechanical ventilation from studies without a VAP prevention method under study were labelled as observational groups. The studies of intervention studies were classified as follows. The non-TA based methods of VAP prevention used interventions other than topical antibiotics. These were usually delivered at either the gastric, airway or oral sites. The SDD studies were further sub-classified as to whether the control group was concurrent and co-located within the same ICU as the intervention group (concurrent control) or not (non-concurrent).
7. The component (control and intervention) groups were decanted from each study as follows;

- The control and intervention groups from non-TA based methods were classified as indicated in the original study
- Among studies of SDD, all groups that received prophylaxis with any regimen of topical antibiotic, whether or not an anti-fungal was included in the regimen, were designated as an SDD intervention group and all other groups from SDD studies were classified as a control group.

Data extraction

The RT *Candida* is the number of patients with *Candida* isolates from respiratory sampling per 100 patients with prolonged (>24 hours) stay in the ICU whether or not VAP has been documented. In addition, the following were also extracted where available; the overall incidence proportion of VAP, the incidence of candidemia, the incidence of *Candida* colonization at non-respiratory tract sites without regard to how this had been defined in each study and the proportion of admissions for trauma. Each of these were expressed as a

proportion using the number of patients with prolonged (>24 hours) stay in the ICU as the denominator. Other parameters extracted were whether the mode of diagnosis of VAP required bronchoscopic sampling and whether topical placebo had been used to achieve observer blinding.

Caterpillar plots

To generate caterpillar plots, the RT *Candida* data were logit transformed for analysis as previously [137]; with the total number of patients as the denominator (D), the number of patients with RT *Candida* as the numerator (N), and R being the RT *Candida* proportion (N/D), the logit(RT *Candida*) is log(N/(D-N)) and its variance is 1/(D*R*(1-R)). Note that for any group with a zero event rate (N=0), the addition of the continuity correction (i.e. N+0·5) is required to avoid indeterminate transformations of mean and variance. Using these pre-calculated logits and logit variances, group specific 95% confidence intervals, summary logits and the associated summary 95% CIs were generated using the 'metan' command in STATA. On the logit scale the 95% confidence intervals for a proportion are symmetrical and remain within the interval of 0 to 100%.

For each category of component group the summary mean logit RT *Candida* and associated 95% confidence interval were calculated using random effects methods. These were then back-transformed to the percentage scale. The benchmark is the summary mean RT *Candida* per 100 patients derived from the observational studies and the benchmark range is the 95% prediction interval.

Bivariate plots and Confidence ellipses

To assess correlation of RT *Candida* with candidemia incidence, the logit transformed data was assessed by two methods; a 95% prediction ellipse [138- 140], and linear regression. The prediction ellipse method enables the correlation as observed in other studies to be benchmarked. The relationship between logit transformed RT *Candida* with year of publication was assessed using locally weighted regression and smoothing scatterplot (LOWESS) [141].

Statistical analysis

A regression model of RT *Candida* proportion was developed using GEE methods as these accommodate any intra-cluster correlation ('xtgee' command in STATA; release 12.0, STATA Corp., College Station, TX, USA). In this analysis, the predictor variables were the component group membership being either membership of a group from an observational study; a control group or; an intervention group; type of intervention under study; the use or non-use of topical placebo and, whether the mode of diagnosis of VAP required bronchoscopic sampling. As a sensitivity analysis the GEE regression model analysis was repeated limited to studies obtained from systematic reviews. In addition to the Poisson model, the GEE regression model was undertaken with a binomial as well as a negative binomial models as additional sensitivity tests.

Results.

Characteristics of the studies

Of the 113 studies identified by the search [1-113], 72 were sourced from 13 systematic reviews and a further 40 sourced from elsewhere (Table 1; Fig. 1). The majority of SDD studies were published in the 1990's and all but four studies of SDD were European in origin. Two studies were supplemented with data from published doctoral theses [76, 113] or related publications [142].The studies are detailed in the Electronic Supplementary Material (ESM) file.

A total of 191 component groups were decanted from these 113 studies with 36 groups from observational studies (ESM file Table S1), 71 groups from studies of various non-TA methods of VAP prevention (ESM file Table S2), and 84 groups from studies of SDD having either a non-concurrent (ESM file Table S3) or concurrent design (ESM file Table S4). Eleven studies had more than one observational, control or intervention group. Two studies had both concurrent and non-concurrent control groups. Group wide risk factors for candidemia were identified in only six studies. Three SDD studies used a regimen not containing an anti-fungal [71, 111, 112].

Candida colonization

A measure of *Candida* colonization not limited to patients with suspected VAP and not limited to respiratory sites was reported for 32 studies including 18 of the SDD studies (Table 1). There was a wide range in this incidence (Fig. S5 & S6) with the incidence among concurrent control ($p = 0.066$; Table S5) groups from studies of SDD being higher versus the incidence in the observational groups.

The incidence of *Candida* colonisation, at sites other than respiratory tract and not restricted to patients with suspected VAP together with candidemia incidence were available from 40 groups from studies of all types. There were too few groups to discern a significant relationship between these incidences or to generate a robust prediction ellipse using the non-TA studies (Fig. S5).

RT *Candida* incidence

The mean RT *Candida* incidence among the 36 observational groups is 1·3 (95% confidence interval; 0·9-1·8%) (ESM file Fig. S1). This is the RT *Candida* benchmark. There was no significant trend in RT *Candida* incidence by year of study publication and a LOWESS line is presented (Fig. 2). Twenty-three of the 32 control groups of the concurrent control design studies were above this LOWESS line. The mean RT *Candida* incidence among the control groups was significantly higher than in the intervention groups from concurrent design SDD studies (p = 0.001; Fig. S4).

The RT *Candida* incidence was highest amongst the concurrent control groups of the SDD studies versus other types of component group (Fig. 3, ESM file Fig. S1-S4). The effect of membership of the various categories of component group on RT Candida were examined in GEE models of RT Candida together other group level variables (Table 2). The effect of membership of a concurrent control group of an SDD study was significant (p=0.021). The group wide presence of candidemia risk factors (p = 0.001) and the proportion of admissions for trauma (p = 0.004) were also significant factors in the model.

Candidemia

The incidence of candidemia was reported for 101 of the component groups (Table 1, Fig. S7). The incidence among concurrent control ($p = 0.024$) groups from studies of SDD were higher versus the incidence in the observational groups.

Both candidemia incidence and RT Candida incidence data were available from 19 groups from either observational studies or from studies of non-TA methods (Fig. 4a). The scatterplot presenting the bivariate relationship among these 19 groups, together with the linear regression line and a 95% prediction ellipse is shown using logit scales for each axis (Fig. 4a). This linear regression and prediction ellipse are in turn used to benchmark the groups from the studies of SDD (Fig. 4a-c). Whilst most of control groups from studies of SDD with a non-concurrent (Fig. 4b) and concurrent design (Fig. 4c) are within this benchmark prediction ellipse, shift to the right and upward is apparent for the control groups in the latter plot (Fig. 4c).

Discussion

This is a meta-analysis of the incidence of respiratory tract colonization with *Candida* (RT *Candida*) among ICU patients receiving mechanical ventilation within studies in the literature. This analysis has examined the relationship between RT *Candida* and candida colonization at other sites and also with candidemia as well as the relative importance of selective digestive decontamination (SDD) versus other candidate risk factors towards it. Only 45 of the studies are common to this meta-analysis and to the previous meta-analysis of candidemia [121]. This previous meta-analysis [121] was not restricted to the patient population receiving mechanical ventilation and had included a higher proportion of studies with group wide risk factors for candidemia (25 of the 103 studies [121]) versus only six of the 113 studies included here. As a consequence, there is a lower incidence of candidemia among the studies here versus previously [121]. However, even within this differently selected set of studies, the incidence of candidemia is again found to be higher among the control groups of SDD studies with a concurrent design than any other type of component group (Table 1).

There is a higher incidence of both *Candida* colonization at respiratory (RT candida) and other sites among the control groups of SDD studies with a concurrent design versus other groups (Table 1). This higher incidence of RT candida cannot be explained by year of publication (Fig. 2), nor in regression models that include the group wide presence of risk factors for candidemia or proportion of trauma admissions or mode of respiratory sampling (Table 2).

There is a correlation between candidemia and RT *Candida* among the studies here for which data is available (Fig. 4). However the relationship between RT *Candida* and candidemia is more complex than a simple linear correlation for the following reasons. Candidemia, with an incidence of approximately 1% amongst ICU patients [121], is a rare outcome and studies with fewer than 100 patients may have one or no cases [143-149]. The relationship described here is at the group level rather than at the patient level. In relation to non-respiratory *Candida* colonization, the patient level association has recently been examined in a multi-center study [150]. The relative risk for invasive candidiasis in the mechanically ventilated ICU patient population differs for throat, perineum and urine sites of colonization and also for different sampling time points [150]. Measures of non-respiratory *Candida* colonization among the studies here were poorly documented in relation to exact sites and timings and in any case was available from less than half of the studies surveyed.

It should be noted that the clinical significance of RT Candida is unclear [151-157] and current consensus guidelines recommend against its specific treatment in the absence of either clear histological evidence for pulmonary infection, which is rare [147-149], or evidence of invasive disease [114, 115]. However, *Candida* colonization continues to remain of interest from both the individual and the population perspective.

At the level of the individual, the clinical significance remains unclear with conflicting results of studies of *Candida* colonization of the respiratory tract among ICU patients. Some investigators have found that *Candida* colonization of the respiratory tract is associated with a worse outcome [151] in association with evidence of increased systemic inflammation [152]. However a subsequent pilot study of antifungal therapy for RT

candida did not find sufficient evidence of benefit to justify proceeding to a full scale controlled trial [153]. By contrast, other workers have not found an association with a higher mortality risk [145, 154] in ICU patients even though there were higher disease severity scores or degree of organ dysfunction at ICU admission. Moreover no apparent outcome benefit associated with the use of empiric systemic anti-fungal therapy in this patient group was found in either this study [154] or in a large multi-center study [155].

From the population perspective, *Candida* colonization is an important constituent of the ICU microbiome. RT candida could increase the risk for co-infection with antibiotic resistant bacteria in the airway [156] through molecular interactions with bacterial pathogens [117] for which anti-fungal therapy may be protective [118].

RT Candida has potential use as a more readily available indicator for benchmarking *Candida* colonization incidence in the patient group receiving mechanical ventilation. RT Candida is used here for this purpose so as to benchmark *Candida* colonization across different studies that have examined a variety of interventions whether using TA based regimens such as SDD or non-TA based methods for VAP prevention.

The effect of SDD on Candida colonization is unclear. On the one hand, SDD as a regimen comprising topical antibiotic and anti-fungal agents appears to be protective against fungal colonization, infection and possibly even mortality [119,120]. Indeed the protection derived by SDD appears to outperform that obtained using azole antifungal prophylaxis in this patient group [120]. On the other hand, this protection is not apparent in the largest study which had a non-concurrent design [157]. Moreover, SDD may have complex effects on the ICU microbiome. Indeed, in the first SDD study [74, 142] it was asked whether this

indirect effect of SDD might confound any attempt to estimate the direct effects using a conventional concurrent study design.

An uncalibrated analysis of the available *Candida* colonization data, whether as RT candida or as *Candida* colonization not restricted to respiratory sites and not restricted to patients with suspected VAP, are consistent with what appears to be a near halving in colonization incidences, as implied in the meta-analyses of the concurrent design SDD studies [119, 120]. However on closer scrutiny and using the RT candida benchmark for calibration, the true impact of SDD on the incidences of *Candida* colonization as well as on candidemia would appear to be a near doubling amongst the concurrent control groups of SDD studies (Table 1). This occurs presumably as a result of an indirect contextual effect through inapparent cross infection [158]. By contrast, the effect of SDD on RT candida in studies that are non-concurrent is insignificant (table 2), as observed elsewhere [157].

It is not the intention here to examine the substantial number of different SDD regimens but rather the component groups from the two broad categories of TA and non-TA studies. In any case, it should be noted that complete *Candida* decolonization using SDD is difficult to achieve [159, 160]. Two recent studies of ICU patients that were colonized with *Candida* and were receiving SDD provided conflicting evidence that the administration of nebulised amphotericin additional to SDD might confer clinical benefit [159] versus harm [160]. Of note in both studies, the time to achieve 50% decolonization with the addition of nebulised amphotericin to the standard SDD regime was five days in both studies. By contrast, among a multi-center study of 3000 ICU patients colonized with *Candida*

receiving routine systemic antifungal therapy with a mean ICU stay of 5 days, typically between 40 and 50% remain colonized on ICU discharge [161].

There are four specific challenges in undertaking an analysis of RT Candida. The potential for transmission of *Candida* between control and intervention group patients in the same study renders the presumption of independence of RT Candida events untenable [162].

Second, for most SDD studies the primary end point was VAP occurrence and RT Candida was an occasional secondary end point. How studies with zero RT Candida events are optimally included in any analysis is important to the conclusions. Studies with zero RT Candida events should not be overlooked as they provide potential evidence against a contextual effect. However, the majority of the SDD studies were smaller than 60 patients and, being a rare event (<2% in most studies), a zero RT Candida event rate is unsurprising. As a consequence, the upper 95% confidence intervals for these groups are non-trivial in caterpillar plots (Fig S1-S4). Note that for a group of size N=60 with zero events the upper 95% confidence can be approximated by the 'rule of three' as 5% (= 3/N) [163].

Thirdly, to quantify a contextual effect requires a calibration to a benchmark range derived using for reference data from studies from comparable target populations. The final issue is one of validity: does RT Candida correlate with a clinically relevant and commonly reported end point?

To deal with the first and third of these challenges, GEE based analytic strategies have been used here to model the RT Candida of both control and intervention groups of all

studies within a single analytic model as a statistical calibration (Table 2). There is an upward dispersion in RT Candida incidence among concurrent control groups from SDD studies away from this benchmark (Fig. 3). This upward dispersion is apparent in the GEE models as positive coefficients in association with membership of concurrent control groups within studies of SDD/SOD (Table 2).

To deal with the second and third issues, the continuity correction has been used to enable zero event groups to be represented on the logit scale which enables several types of graphical display for the purposes of a visual calibration (Figs. S1-4; Fig. 3). Moreover the validity issue is able to be addressed through an examination of the bivariate relationship between RT candida and candidemia (Figs. 4a-c). The visual analysis of the bivariate relationship is aided by the use of a 95% prediction ellipse in the plots, a method which is better suited to this purpose than linear regression [138-141]. All of these visual displays dramatically reveal that the component groups of all types, with the exception of those concurrent control groups from studies of SDD, each have a distribution similar to the observational groups from which the benchmark was derived. Strikingly even the distribution of the intervention groups of the SDD studies are similar to those from which the benchmark was derived. This would imply that any apparent effect of SDD on Candida colonization and Candidemia within concurrent control design studies is not explainable as simply a direct anti-fungal prevention effect occurring within the intervention group (Fig. S7).

There are several limitations to this study. This is an analysis at the group level and is unable to take account of patient specific risk factors for RT Candida. For example, the usage of empiric (non-protocolized) antifungal therapy in each study is an important

unknown as non-use may account for vulnerability to RT Candida at the individual level. However, it is unlikely that such unidentified patient level risk factors would be able to account for the discrepancies noted here. Such a putative patient level risk factor would need to be a consistently strong risk factor for RT Candida across all the studies and yet also be profoundly unevenly distributed, predominating in the groups of the SDD studies versus other groups within the broader evidence base examined here.

Another limitation is the imprecision associated with the diagnosis of VAP which may lead to the potential for observer detection bias of RT Candida. That the mode of VAP diagnosis and the use of topical placebo were not significant factors in the regression model (table 2) implies that this bias is likely to be minimal. Moreover, topical placebo use can be taken as a surrogate indicator of a study that was observer blinded. A further limitation is the question of non-reporting of RT Candida amongst potentially eligible studies. However, the correlation between RT Candida and candidemia provides some validation at least amongst those studies for which both data were available.

It is never possible to be certain that every relevant study has been obtained in a literature search or that the search has been truly adequate. Restricting the analysis to those studies obtained from systematic reviews attempts to provide the basis for an analysis of data derived through an independent and transparent search. That the findings of such a restricted analysis are similar to the full analysis would imply that the search has been adequate and that the number of missing studies required to alter the findings would need to be substantial.

Conclusion

The RT Candida incidence within observational groups of mechanically ventilated patients is 1.3% (this is the RT Candida benchmark). The incidence of RT candida and candidemia are correlated. There is insufficient information to discern how closely *Candida* colonization at other sites is correlated with candidemia. At the group level, the presence of candidemia risk factors, the proportion of trauma admissions and membership of a concurrent control group within an SDD study are each risk factors for RT Candida. The apparent protection against *Candida* colonization from the use of SDD appears spurious as the incidence of both RT candida and colonization at other sites is higher among concurrent control groups of SDD studies than among observational and indeed other types of component group. These observations, as with similar observations for VAP [123], candidemia [121] and bacteremia [122] incidences among these studies, are paradoxical. Apart from major publication bias, or the effect of any major and as yet unidentified and mal-distributed patient level risk factors for RT Candida, these profound discrepancies indicate a major contextual hazard associated with the topical antibiotic component of SDD on RT Candida within studies with concurrent controls. These increased incidences would be inapparent within individual SDD studies examined in isolation [158].

Abbreviations;

ICU, Intensive Care Unit; MV, Mechanical Ventilation ; SDD, selective Digestive Decontamination; VAP, Ventilator associated pneumonia; RT Candida, *Candida* among patients with Ventilator associated pneumonia

441 Additional material

442 ESM file: RT Candida data for observational studies (Table S1), studies of non-TA-based
443 methods of VAP prevention (Table S2), studies of SDD with non-concurrent
444 groups (Table S3) and studies of SDD with concurrent groups (Table S4).
445 Caterpillar and other plots of RT Candida data (Fig. S1-S7).
446

Competing interests

James Hurley declares that he has no competing interests.

Author contributions

As sole author, JH produced the design of the study, performed the statistical analysis and wrote the manuscript. JH read and approved the final manuscript.

Compliance with Ethical Standards

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Ethical approval: This article does not contain any studies with human participants performed by the author.

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991 **Table 1. Characteristics of studies** [a]

	Observational studies	Groups of interventional studies of VAP prevention		
		Methods other than topical antibiotics	SDD	
			Non-concurrent	concurrent control
Study characteristics				
Sources [ref]	Table S1 [112-114]	Table S2 [115-120]	Table S3 [93-98]	Table S4 [93-98]
Number of studies	34	35	9	33
Origin from systematic review	6	17	4	29
EU origin [b]	19	23	7	31
MV for >48 hours for <75% [c]	4	1	2	2
Trauma ICUs [d]	4	5	3	8
Bronchoscopic sampling [e]	18	13	6	13
Group wide candidemia risk factors [f]	0	0	2	4
Study publication year (range)	1987-2014	1987-2014	1987-2014	1987-2007
Group characteristics				
Numbers of patients per study group; median (IQR) [g]	233 108-591	96 51-184	91 50-127	51 31-101
VAP incidence per 100 patients; (median; IQR; number of groups) [g]				
Cohort	20·4%; 14·1–31·0% (36)		NA	NA
Control	NA	20·6%; 14·8-26·5% (34)	45·5%; 23·0-59·3% (7)	30·4%; 18.5-48·1% (32)
Intervention	NA	13·2%; 9·0-21·7% (34)	10·1%; 7·6 – 16·7 (11)	11·8% 5·6-23·0% (35)

Table 1 (continued)

	Observational studies	Groups of interventional studies of VAP prevention		
		Methods other than topical antibiotics	SDD	
			Non-concurrent control	concurrent control
Candidemia per 100 patients; mean; 95% CI (number of groups) [h]				
Cohort	0·8%; 0·2–2·9% (6)			
Control		0·8%; 0·8-1·6% (5)	0·7%; 0·3-2·0% (5)	1·4%; 1·0- 1·8% (28)
Intervention		0·8%; 0·4-1·6% (8)	0·8%; 0·4-1·8% (10)	1·2%; 0.9-1·7% (29)
Overall *Candida* colonization per 100 patients; mean; 95% CI (number of groups) [i]				
Cohort	9·7%; 3·0–27·0% (7)			
Control		4·8%; 1·1-18·6% (7)	9.8%; (1)	25·9%; [j] 12·8-45·5% (16)
Intervention		2·7%; 0·8-8·4% (7)	4·3%; 0·4-33·0% (4)	9·4%; [j] 4.3-19·1% (19)
Respiratory *Candida* per 100 patients mean; 95% CI (number of groups) [k]				
Cohort	1·3%; 0·9–1·8% (36)			
Control		1·4%; 1·2-1·6% (33)	0.7%; 0·4-1·4% (6)	2·3%; 1·6-3·4% (32) [l]
Intervention		1·0%; 0·7-1·4% (33)	1·3%; 0·5- 3·0% (9)	1·4%; 1·0- 1·9% (35) [l]

Footnotes to table 1

a. Abbreviations; ICU, Intensive care unit; MV; EU, European Union; Mechanical ventilation; NA not applicable; SDD , Selective Digestive Decontamination; VAP ventilator associated pneumonia; IQR, interquartile range

b. Originating from a member state of the EU as at 2010 or Switzerland or Norway

c. Studies for which less than 75% of patients were reported to receive more than 48 hours of mechanical ventilation.

d. Trauma ICU defined as an ICU with >50% of patient admissions for trauma

e. Bronchoscopic versus tracheal sampling toward the diagnosis of VAP

f. One or more of the following risk factors were used for patient inclusion; use of TPN; major gastro-intestinal surgery or perforation; or liver transplantation

g. Calculated including only groups for which >75% received >48 hours of MV

h. See Fig. S7.

i. *Candida* colonization not limited to patients with suspected VAP and not limited to respiratory sites. See Fig. S6

j. Difference between intervention versus control groups from studies of SDD with concurrent design in a marginal analysis of the GEE model (as in Table S5) ; p=0.001

k. *Candida* colonization limited to patients with suspected VAP and limited to lower respiratory sites.

l. Difference between intervention versus control groups from studies of SDD with concurrent design in a marginal analysis of the GEE model (as in Table 2) ; p=0.051

Table 2: Logit RT *Candida* incidence; generalized estimating equation models (all groups) [a]

Factor	Coefficient [b]	95% CI	p
Groups from observational studies (reference group)	-4·31	-4·77 to -3·85	<0·001
Control groups			
• Non-TA [c]	+0·16	-0·32 to +0·64	0·51
• SDD/SOD; non-concurrent	+0·10	-0·86 to +1·06	0·84
• SDD/SOD; Concurrent [d]	+0·56	+0·08 to +1·04	0·021
Intervention groups			
• Non-TA	-0·02	-0·54 to +0·50	0·93
• SDD/SOD; non-concurrent	+0·26	-0·45 to +0·98	0·47
• SDD/SOD; Concurrent [e]	+0·12	-0·38 to +0·62	0·63
Candidemia risk factor	+1·40	+0·78 to +2·01	0·001
Trauma [f]	+0·007	+0·02 to +0·01	0·004
Year of publication [g]	-0·003	-0·02 to +0·02	0·82
EU origin	-0·06	-0·42 to +0·30	0·74
topical placebo use	+0·05	-0·31 to +0·40	0·80
Mode of diagnosis [h]	-0·19	-0·48 to +0·11	0·21

Footnotes

a. This table displays the results of analysis using the Poisson model for the GEE model. The results obtained from a binomial model are similar (data not shown). Repeating the analysis excluding the three studies of SDD that did not include an anti-fungal within the SDD regimen failed to alter the findings here (data not shown).

b. Interpretation. The reference group is the observational study (benchmark) groups and this coefficient equals the difference in logits from 0 (a logit equal to 0 equates to a proportion of 50%; a logit equal to -4.33 equates to a proportion of 1.3%) and the other coefficients represent the difference in logits for groups positive for that factor versus the reference group.

c. Abbreviations; TA, topical antibiotic; SDD/SOD, selective digestive decontamination / selective oro-pharyngeal decontamination.

d. Repeating the base model with the analysis limited to component groups from studies cited in systematic reviews results in this coefficient becoming +0·67; +0·08 to +1·27; p=0·026

e. Repeating the base model with the analysis limited to component groups from studies cited in systematic reviews results in this coefficient becoming +0·01; -1.07 to +1·07; p=0•99

f. The co-efficient for trauma represents the increment in logit for each percentage point increase in the proportion of admissions for trauma

g. The co-efficient for year of publication represents the increment in logit for each year after 1985

h. For sampling using bronchoscopic versus tracheal sampling

Figure legends.

Fig. 1 Search method, screening criteria and resulting classification of eligible studies and subsequent decant of component groups. The seven numbered arrows to the right represent steps in the process as discussed in the methods; steps one – five refer to studies and steps six- seven refer to component groups decanted from the studies being control (rectangles) and intervention (ovals) groups from ICU based studies of infection prevention methods and observation groups from cohorts of ICU patients without a prevention method under study (diamond). The horizontal dotted rectangles represent the group contrasts used toward the calculation of the contextual effects of the component groups each versus the observation groups as the reference category. Note; the total numbers do not tally as some systematic reviews provided studies in more than one category and some studies provided groups in more than one category. Note; SDD includes SOD and other methods based on the use of a topical antibiotic (TA)

Fig. 2 RT Candida incidence versus year of publication. Scatter plot of RT Candida incidence in observational groups (open black circles) versus year of study publication for which the linear regression was non-significant ($p = 0.72$) and hence a LOWESS regression line is given. Also shown are the control groups from studies of non-TA methods (open blue triangle) and also concurrent control (CC) studies of SDD/SOD (closed red triangles). Note that the symbols are proportional to group size and the y axis is a logit scale

Fig. 3 Scatter plots of RT Candida incidence. Scatter plots of RT Candida incidence in component (C = control; I = intervention) groups of non-TA and non-concurrent (NCC), and concurrent control (CC) studies of SDD (antibiotic methods) of VAP prevention (blue symbols). The benchmark RT Candida is the summary mean (central broken vertical line)

derived from the observation studies (black symbols) together with the 95% prediction intervals (benchmark range; outer broken vertical lines). Studies with MV for >48 hours for <75% and one outlier study [84] are not shown. Note that the x axis is a logit scale and that studies with a zero RT Candida can only be shown on this plot through use of the continuity correction. These data are displayed in more detail as caterpillar plots (Fig. S1-S4)

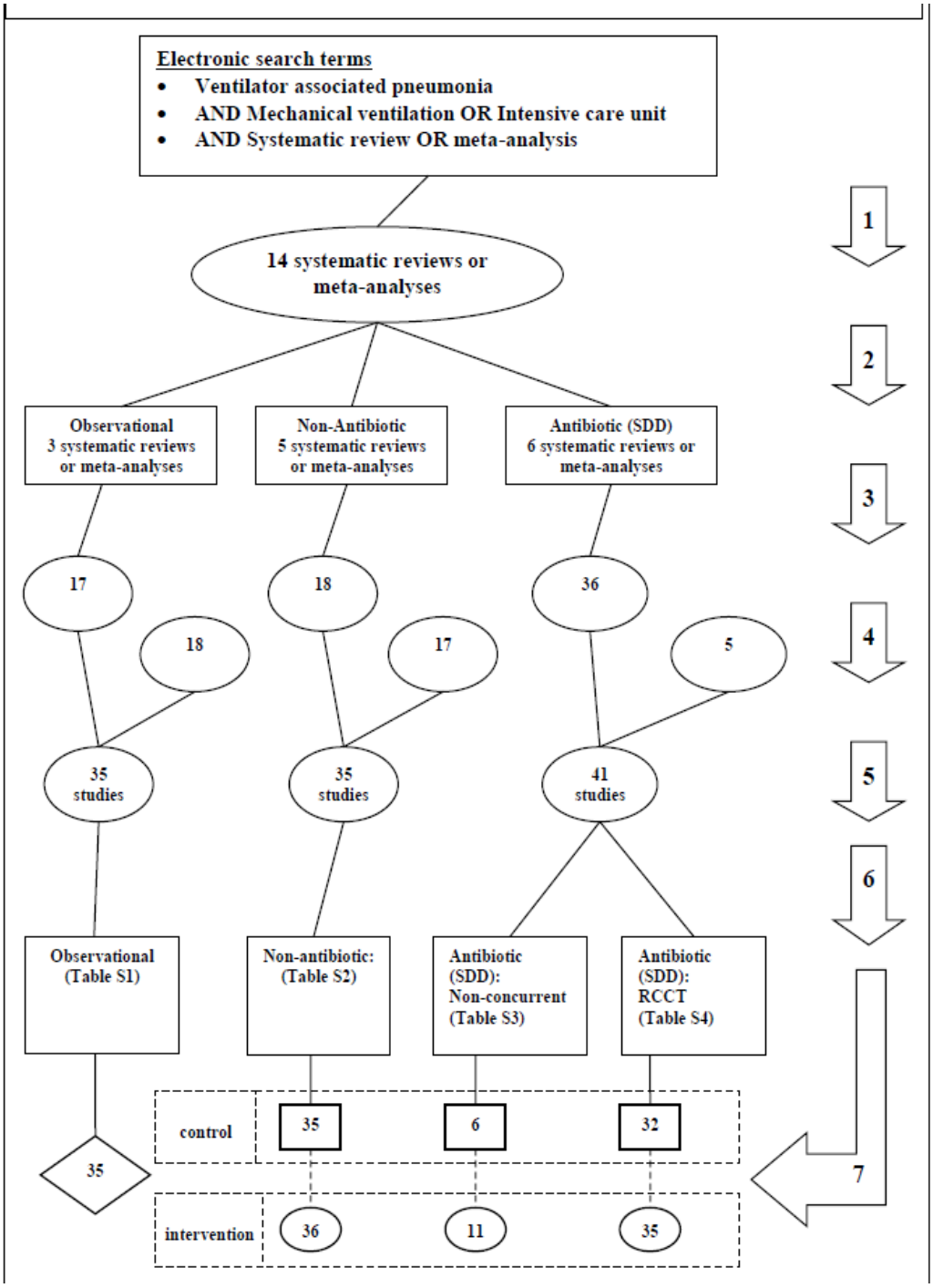
Fig. 4 Candidemia incidence versus RT Candida.

Fig. 4a Scatter plot of Candidemia incidence versus RT Candida incidence in observational groups and control groups from studies of non-TA methods (open black circles) for which both data were available. Both a linear regression ($p = 0.057$) and a 95% prediction ellipse based on these groups are shown. Also shown are the intervention groups from studies of non-TA methods (closed triangles). Also shown are the mean (central) and 95% prediction lines (outer) derived for the full set of benchmark groups for both RT candida (vertical) and candidemia (horizontal). Note that both the x and the y axes are a logit scale

Fig. 4b Scatter plot of Candidemia incidence versus RT Candida incidence in control (closed green triangles) and intervention (open green triangles) groups from studies of non-concurrent design studies of SDD (open green triangles) for which both data were available. The linear regression, 95% prediction ellipse and mean and 95% prediction lines from Fig. 4a are shown for reference

Fig. 4c Scatter plot of Candidemia incidence versus RT Candida incidence in control (closed green triangles) and intervention (open red triangles) groups from studies of concurrent design studies of SDD (open red triangles) for which both data were available.

The linear regression, 95% prediction ellipse and mean and 95% prediction lines from Fig. 4a are shown for reference. Note that one outlier study [84] is not shown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• AND Mechanical ventilation OR Intensive care unit
• AND Systematic review OR meta-analysis
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Observational 3 systematic reviews or meta-analyses
Non-Antibiotic 5 systematic reviews or meta-analyses
Antibiotic (SDD) 6 systematic reviews or meta-analyses
17
18
18
17
36
5
35 studies
35 studies
41 studies
Observational (Table S1)
Non-antibiotic: (Table S2)
Antibiotic (SDD): Non-concurrent (Table S3)
Antibiotic (SDD): RCCT (Table S4)
control
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intervention
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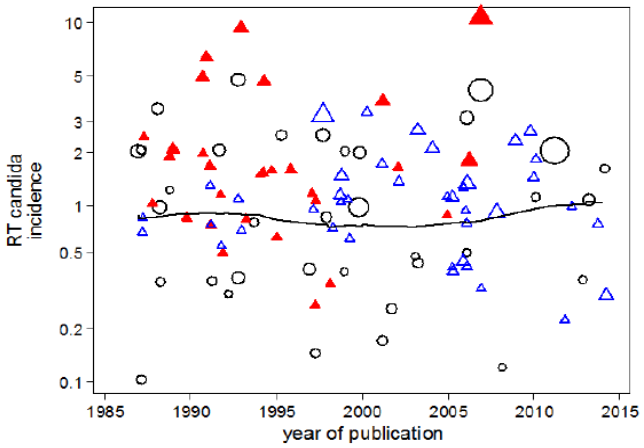
Figure 2


RT candida incidence
10
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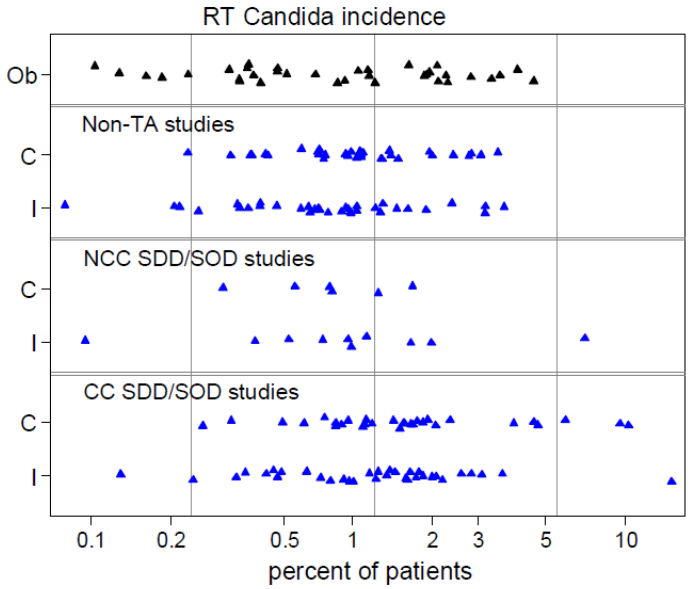
0.5
0.2
0.1
1985
1990
1995
2000
2005
2010
2015
year of publication

Figure 3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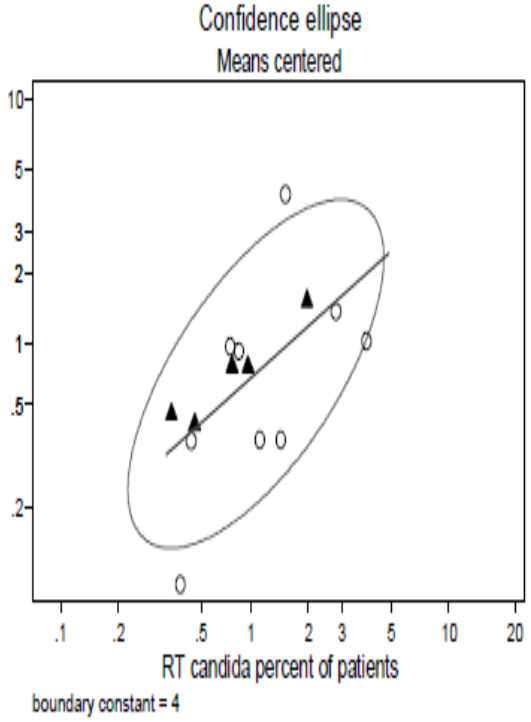
percent of patients

Figure 4a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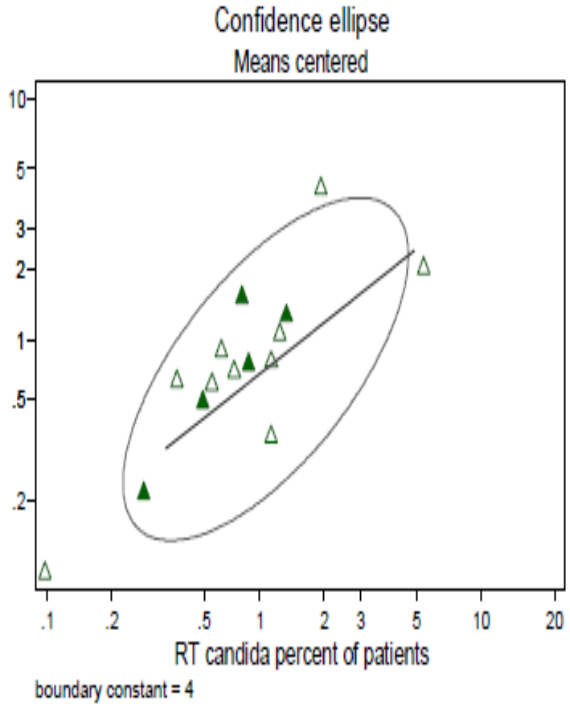
RT candida percent of patients
boundary constant = 4

Figure 4b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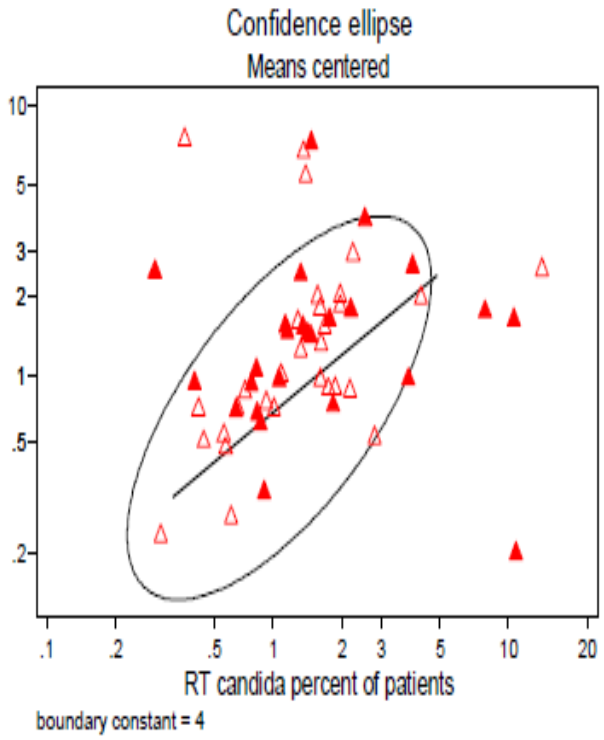
RT candida percent of patients
boundary constant = 4

Figure 4c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20
RT candida percent of patients
boundary constant = 4

Author/s:
Hurley, JC

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