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Editorial

Support for antibiotic prophylaxis during targeted temperature management after cardiac arrest: Heating up or cooling down?

Early-onset pneumonia, diagnosed within 4 days of initiating mechanical ventilation, occurs in up to 63% of resuscitated patients.[1] Pneumonia after cardiac arrest is due to aspiration of gastric contents during cardiopulmonary resuscitation or to introduction of oropharyngeal flora into the lungs during airway management.[2] The risk is increased by post-resuscitation immune paralysis, intestinal mucosal disruption due to ischemic-reperfusion injury, pulmonary contusions, and chest wall dysfunction from rib and sternal fractures.[3,4] The incidence of pneumonia during post-resuscitation cardiac arrest care exceeds the 9–27% incidence in the general critical care population, but is similar to patients admitted with structural coma of other etiologies.[5–7]

Infection during post-resuscitation cardiac arrest care has been associated with increased intensive care unit[1,8,9] and hospital length of stay,[10] prolonged duration of mechanical ventilation,[1,8,9] need for rehabilitation,[8] tracheostomy tube placement,[10] worse functional outcomes,[11] and increased mortality.[12] Conversely, some studies have shown that infection is associated with reduced mortality and better functional outcome.[13,14] These paradoxical findings are likely due to immortal time bias (i.e., those who survive long are more likely to develop infection than those who die earlier) rather than any benefit from developing an infection.[15]

Administration of prophylactic antibiotics is a promising strategy to reduce the risk of infection after cardiac arrest. This practice is supported by randomized-controlled trials in heterogeneous cohorts of comatose brain-injured patients (e.g., stroke, seizure, traumatic brain injury, and cardiac arrest). For example, Sirvent and colleagues found that two doses of 1500 mg of cefuroxime administered 12 h apart reduced the incidence of early-onset pneumonia from 36% to 16% ($p = 0.022$),[6] while Acquarolo and colleagues reported that 3 g of ampicillin–sulbactam administered every 6 h for 3 days reduced the incidence of early-onset pneumonia from 57.9% to 21% ($p = 0.022$).[7] Recent observational studies have supported these findings.[16,17] Studies including cardiac arrest patients only have been published recently and the stage has been set for a structured evaluation of the evidence.

In this issue of *Resuscitation*, Couper and colleagues sought to examine the effect of early or prophylactic antibiotic administration during post-resuscitation cardiac arrest care by conducting a systematic review and meta-analysis of the literature.[18] Observational or interventional studies of early (within 6 h to 7 days of admission) or prophylactic antibiotic administration compared to delayed or clinically driven administration were evaluated. Eleven studies including 6149 patients were included in the qualitative analyses and ten studies were included in the quantitative analyses. The investigators found antibiotic administration was not independently associated with survival (OR 1.16, 95% CI 0.97–1.40; $p = 0.11$), good neurological outcome (OR 2.25, 95% CI 0.93–5.45; $p = 0.07$), intensive care unit length of stay (mean difference −0.6, 95% CI −3.6 to 2.4), duration of mechanical ventilation (mean difference −2.5, 95% CI −8.8 to 3.9), or incidence of pneumonia (OR 0.58, 95% CI 0.23–1.46). The quality of evidence was described as low or very low, and heterogeneity (Higgins I^2 statistic) varied substantially (0–83%). The investigators concluded that available evidence does not support the administration of prophylactic antibiotics during post-resuscitation care.

Couper and colleagues should be commended for attempting to answer an important clinical question, and conducting a thorough review of the existing literature, but their findings and conclusions should be interpreted with caution. Most analyses were based on very low quality of evidence. Furthermore, two of the three randomized-controlled trials (RCT's) included have been published in abstract form only (Bongaerts and Daix), and the third RCT (Ribaric) was a pilot study designed to examine the severity of the systemic inflammatory response after cardiac arrest. An analysis of their methodology, including sample size calculation, is therefore not possible. Finally, little information was available regarding antibiotic administration and combining studies that administered antibiotics within 6 h with those administering them within 7 days introduces significant heterogeneity.

The overall treatment effect must also be critically evaluated. The investigators pooled results from both randomized and non-randomized studies, an approach not recommended by The Cochrane Collaboration.[19] Forest plots with results stratified by study design were included, but complete data were only available for survival, good neurological outcome, and incidence of pneumonia. Observational studies with unadjusted analyses showed increased survival (OR 1.91. 95% CI 1.07–3.40; $p = 0.03$) with early or prophylactic antibiotics, while those with adjusted analyses showed better neurological outcome (OR 11.56, 95% CI 5.19–25.74; $p < 0.00001$). These findings must be interpreted in the context of the inherent risk of bias in observational studies and the wide confidence intervals shown.

Overall, the appropriateness of the meta-analysis can be questioned, but the literature review is valuable, and highlights the paucity of evidence supporting or refuting antibiotic prophylaxis.

We look forward to the publication of the full results of the Antibiotherapy during Therapeutic Hypothermia to Prevent Infectious Complications (ANTHARTIC). ANTHARTIC randomized 196 adults to amoxicillin–clavulanic acid (1 g/ 200 mg) or placebo 3 times a day for 2 days after resuscitation from out-of-hospital cardiac arrest due to an initial shockable rhythm.[20] Based on their published abstract, the incidence of early-onset pneumonia was significantly reduced (HR = 0.546, 95% CI 0.315-0.946), but 28-day mortality was unchanged (41.4% vs 37.5%). Although the ANTHARTIC trial will be the highest quality data available when published in full, several methodologic aspects of the trial need to be considered. First, their definition of early-onset pneumonia (< 7 days) differs from previous studies, which have defined it as occurring within 4 days.[6,7] Second, the prophylactic antibiotic studied (intravenous amoxicillin–clavulanic acid) is not available in all countries, including the United States. Third, their analysis of 28-day mortality rather than good neurological outcome leaves the critical issue of long-term functionality unaddressed. Fourth, patients with non-shockable rhythms were excluded, limiting the external validity of the trial. Finally, the trial is likely underpowered, since the effects of infection on mortality and functional outcomes after cardiac arrest are likely modest, compared to neurological and circulatory cases of death, and a large trial will be needed to answer the question.

Pneumonia after resuscitation from cardiac arrest is a major clinical problem, and a trial of antibiotic prophylaxis is needed. Such a trial should have standardized definitions, include the subpopulation most likely to be helped by therapy, include patients with both shockable and non-shockable initial heart rhythms, evaluate early-onset pneumonia within 4 days, and assess functional outcome at hospital discharge and delayed follow-up. The antibiotic studied should be widely available, well tolerated, microbiologically appropriate, and unlikely to induce resistance. Patients with a strong indication for antibiotic treatment should be excluded. Finally, the trial should be powered to determine a significant difference in functional outcomes, not just early-onset pneumonia — likely necessitating thousands of patients. As such, it is an appealing pragmatic trial for a large clinical trials group to undertake.

So - is the support for antibiotic prophylaxis during post-resuscitation cardiac arrest care heating up or cooling down? The systematic review and meta-analysis by Dr. Couper and colleagues highlights the question, defines some of the associated issues, and describes what has been studied to date, but a definitive answer as to how clinicians should proceed at the bedside will have to wait until the quality of evidence is just right.

Conflicts of interest

The authors report no conflicts of interest.

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