

CONGRESS REPORT

An update on the 27th Annual ESICM congress: Hot Topics session

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Introduction

The most eagerly awaited session of the 27th Annual Congress of the European Society of Intensive Care Medicine (ESICM), held in Barcelona, was beyond doubt the Hot Topics session on 1 October 2014. Results from six long-awaited scientific trials were presented for the first time and concurrently most of the corresponding papers were simultaneously published in major medical journals. The sessions were led by the current ESICM President Daniel De Backer and JAMA Editor-In-Chief Howard Bauchner. In summary, the following study results were presented at the Hot Topics session:

- The effects of decontamination of the oropharynx and intestinal tract on antibiotic resistance in intensive care units (ICUs), presented by the first author, Evelien Oostdijk, from Utrecht (the Netherlands)
- The VITdAL@ICU trial: Correction of vitamin D deficiency in critically ill patients, presented by the first author, Karin Amrein, from Graz (Austria)
- Early high-dose erythropoietin therapy after out-of-hospital cardiac arrest: a multicentre, randomised controlled trial (EPO-ACR 02), presented by the first author, Alain Cariou, from Paris (France)
- Early goal-directed therapy in sepsis: the ARISE trial, presented by Sandra Peake from Adelaide (Australia)
- Transfusion threshold in septic shock: the TRISS trial, presented by Lars Holst from Copenhagen (Denmark)
- Calories: A phase III multicentre RCT comparing early nutritional support with parenteral vs. enteral routes, presented by Kathryn Rowan from London (United Kingdom)

Effects of decontamination of the oropharynx and intestinal tract on antibiotic resistance in ICUs

Evelien Oostdijk discussed her trial evaluating the effects of decontamination of the oropharynx and intestinal tract on

antibiotic resistance in Dutch ICUs. The aim of the study was to evaluate the effect of selective decontamination of the digestive tract (SDD) and selective oropharyngeal decontamination (SOD) on both patient outcome and antibiotic resistance. The study was designed as a cluster randomised crossover trial comparing one year of SOD with one year of SDD in 16 Dutch ICUs between 2009 and 2013. Patients with an expected length of ICU stay longer than 48 hours were eligible to receive SOD or SDD. A staggering number of 5881 and 6116 patients were included in the clinical outcome analysis for SOD and SDD, respectively. The primary outcome was prevalence of antibiotic-resistant Gram-negative bacteria, whereas the secondary outcomes were 28-day mortality, ICU-acquired bacteraemia, and length of ICU stay. Not surprisingly, SDD was associated with a lower prevalence of antibiotic-resistant Gram-negative bacteria in perianal swabs when compared with SOD. For aminoglycoside resistance, average prevalence was 5.6% during SDD and 11.8% during SOD ($p < 0.001$). However, although resistance was markedly lower during SDD than SOD, there was a gradual increase observed with aminoglycoside-resistant Gram-negative bacteria, which was most pronounced during the SDD study period. This could result from the selective effects of tobramycin on antibiotic-resistance genes in the human microbial flora, with proliferation of resistance genes in the anaerobic flora. The authors acknowledged that future studies are needed to address the carriage with antibiotic-resistant bacteria after discontinuation of SDD and SOD. The resistance to aminoglycosides is a major concern since it increases the likelihood of acquisition of colistin resistance. However, the prevalence of resistance to colistin was less than 1.1% in rectal swabs and 0.6% in respiratory samples during SDD and even lower during SOD. Furthermore, careful monitoring of endotracheal aspirates, oropharyngeal plus rectal swabs, is an essential component of the SDD

strategy and plays a pivotal role in early detection of both aminoglycoside and colistin resistance. Day 28 mortality (2nd outcome) was 24.1% vs. 25.4% during SDD and SOD, respectively ($p = 0.42$). There were no statistically significant differences in other outcomes. In previous trials it was suggested that surgical patients would benefit more from SDD, whereas non-surgical patients would benefit more from SOD. However, in a subgroup analysis the investigators found no difference between these two patient groups in relation to the two treatment strategies. ICU-acquired bacteraemia (mostly *Enterobacteriaceae*) occurred in 5.9% and 4.6% of the patients during SOD and SDD, respectively (odds ratio 0.77 [95% CI, 0.65-0.91]; $p = 0.002$; number needed to treat 77). The authors are in favour of SOD because no differences in survival and length of ICU and hospital stay were found between the two treatment strategies, and because the cost-benefit ratio of SOD seemed more beneficial. However, the authors did not take into account that bacteraemia and sepsis occurred less frequently during SDD with inherent cost reduction. In the last decade SDD or SOD has obtained its place in Dutch ICUs making it standard care with proven efficacy and a good safety record. Hopefully, these results will reduce previous concerns regarding the induction of antibiotic resistance with SDD. Whether the results of this study can be extrapolated to other countries with much higher rates of antibiotic resistance than the Netherlands is still under debate. Currently, a large SDD study is being conducted in several countries besides the Netherlands including some countries with high rates of antibiotic resistance, e.g. France and Spain (R-GNOSIS), from which the results have to be awaited. The current study was simultaneously published online in the Journal of the American Medical Association (JAMA).¹ Surprisingly, the authors of an editorial in the same issue were less hesitant against the use of SOD in ICUs of the United States as opposed to the use of SDD.

Effect of high-dose vitamin D3 on hospital length of stay in critically ill patients with vitamin D deficiency

Karin Amrein presented the results of the VITdAL study, evaluating the role of vitamin D3 in ICU patients.² A low vitamin D status is associated with increased mortality and morbidity in critically ill patients. However, it is unknown whether this relation is causal. The aim of the study was to investigate whether vitamin D3 treatment over six months would affect hospital length of stay (primary outcome) and length of ICU stay, the percentage of patients with 25-hydroxyvitamin D levels higher than 30 ng/ml at day 7, hospital mortality, and six-month mortality (secondary outcome). A total number of 492 patients were randomised to receive vitamin D3 540,000 IU followed by monthly maintenance doses of 90,000 IU for five months or placebo given orally or via nasogastric tube. The median length of

hospital stay was not significantly different between groups (20.1 days) for vitamin D3 vs. 19.3 days for placebo. Hospital mortality and six-month mortality were also not significantly different (hospital mortality: 28.3% for vitamin D3 vs. 35.3% for placebo; six-month mortality: 35.0% for vitamin D3 vs. 42.9% for placebo). For the severe vitamin D deficiency subgroup (< 12 ng/ml) analysis ($n = 200$), length of hospital stay was not significantly different between the two study groups: 20.1 days for vitamin D3 vs. 19.0 days for placebo. However, hospital mortality was significantly lower at 28 deaths among 98 patients (28.6%) for vitamin D3 compared with 47 deaths among 102 patients (46.1%) for placebo (HR, 0.56 [95% CI, 0.35-0.90], $p = 0.04$), but not six-month mortality (34.7%) for vitamin D3 vs. 50.0% for placebo; HR, 0.60 [95% CI, 0.39-0.93], $p = 0.12$). In summary, the administration of high-dose vitamin D3 compared with placebo in critically ill patients with vitamin D deficiency did not reduce hospital length of stay, hospital mortality, or six-month mortality. However, lower hospital mortality was observed in the severe vitamin D deficiency subgroup, but this finding should be considered hypothesis-generating and requires further study.

Early high-dose erythropoietin therapy after out-of-hospital cardiac arrest

Alain Cariou presented the results of the EPO-ACR02 study. The aim was to evaluate if early administration of a high dose of epoetin alpha (EPO) after cardiac arrest resuscitation could improve the neurological outcome compared with standard treatment.³ The primary outcome was the proportion of patients reaching level 1 of the Pittsburgh CPC scale (i.e., no or minor cerebral disability) at day 60. The secondary outcome was hospital mortality and serious adverse events. The study was a multicentre, randomised, controlled simple-blind study in 20 French hospitals. A total number of 476 patients were randomised to receive five injections of 40,000 IU of EPO ($n = 234$) vs. standard care ($n = 242$). EPO was not associated with improved neurological outcome when compared with standard care, nor was it associated with lower mortality. However, EPO therapy was associated with a higher incidence of thrombotic events such as acute coronary in stent thrombosis (29/233 vs. 14/242), which suggests that giving EPO after cardiac arrest may not be a good idea.

Goal-directed resuscitation for patients with early septic shock

Sandra Peake presented the results of the ARISE study.⁴ The aim of the study was to evaluate the effectiveness of early goal-directed therapy (EGDT) in patients with septic shock. The trial was conducted at 51 centres (mostly in Australia or New Zealand). Patients presenting to the emergency department with early septic shock were randomised to receive either EGDT or usual care. Randomisation was required within

two hours after fulfilment of the final inclusion criterion. The primary outcome was all-cause mortality within 90 days after randomisation. A total number of 796 patients were assigned to the EGDT group and 804 to the usual-care group. Patients in the EGDT group received a larger mean volume (1964 ml) of intravenous fluids in the first six hours after randomisation than did those in the usual care group (1713 ml). In line, the EGDT group also received more colloids than crystalloids when compared with the usual care group. Patients in the EGDT group were more likely to receive vasopressor infusions (66.6% vs. 57.8%), red cell transfusions (13.6% vs. 7.0%), and dobutamine (15.4% vs. 2.6%) ($p < 0.001$ for all comparisons). However, at 90 days after randomisation, 147 deaths had occurred in the EGDT group and 150 had occurred in the usual-care group, for rates of death of 18.6% and 18.8%, respectively. There was no significant difference in survival time, in-hospital mortality, duration of organ support, or length of hospital stay. Several study limitations should be addressed. First, the patients in this study had low rates of chronic disease and better functional status, as evidenced by the low proportion of nursing home residents before randomisation, which may explain the lower risk of death compared with the original EGDT trial. Also the high number of patients discharged home (around 80%) may also support the previous notion. Second, elements of the EGDT protocol may have contaminated the usual-care group which may have biased the study results. Third, the time between presentation on the emergency department and randomisation was not mentioned in the study results. All interventions before randomisation such as start of antimicrobial therapy and intravenous fluids are relevant information. Finally, the use of colloids in septic shock has previously been associated with increased mortality and renal failure. This may be of importance since patients in the EGDT group received significantly more colloids than the usual care group.

The results of this study are in line with those of the ProCESS trial published just recently in the *New England Journal of Medicine*⁵, in which investigators also used a resuscitation algorithm that was similar to that used in the original EGDT trial by Rivers.⁶ Although the results from the ARISE study differ from those in the original EGDT trial, they are consistent with previous studies showing that bias in small, single-centre trials may lead to inflated effect sizes that cannot be replicated in larger, multicentre studies. Although the ProCESS study did not directly compare protocol-based EGDT for resuscitation with care that was not protocol-based, the concordance of results between the ARISE study and the ProCESS study suggests that EGDT does not offer a survival advantage in patients presenting to the emergency department with early septic shock. Whether resuscitation protocols with different goals or different individual therapies

in the EGDT bundle offer a survival benefit remains to be determined.

Lower vs. higher haemoglobin threshold for transfusion in septic shock (TRISS trial)

Lars B. Holst presented the results from the TRISS trial.⁷ The aim of the study was to evaluate the benefits and harm of different haemoglobin thresholds for transfusion in patients with septic shock. In this multicentre, parallel-group trial, they randomly assigned patients in the ICU who had septic shock and a haemoglobin concentration of ≤ 9 g/dl to receive 1 unit of leukocyte-reduced red cells when the haemoglobin level was ≤ 7 g/dl (lower threshold) or when the level was ≤ 9 g/dl (higher threshold) during the ICU stay. The primary outcome measure was death by 90 days after randomisation. A total of 503 patients were randomised in the lower-threshold group and received a median of 1 unit of blood (interquartile range, 0 to 3) vs. 497 patients in the higher-threshold group who received a median of 4 units (interquartile range, 2 to 7). Mortality at 90 days was 43.0% in the lower-threshold group, as compared with 45.0% in the higher-threshold group, (relative risk, 0.94; 95% confidence interval, 0.78 to 1.09; $p = 0.44$). The results were similar in analyses adjusted for risk factors at baseline and in analyses of the per-protocol populations. The numbers of patients who had ischaemic events, who had severe adverse reactions, and who required life support were similar in the two intervention groups. The results from this study are in line with the previous study from Hébert et al.⁸, where a liberal transfusion strategy was not superior to a more restrictive transfusion strategy using the same thresholds as the TRISS trial. It could be debated whether the use of leukocyte-reduced red cells had mitigated the potentially detrimental effects in the higher threshold group.

Trial of the route of early nutritional support in critically ill adults (CALORIES trial)

Kathryn Rowan presented the results from the CALORIES trial.⁹ The authors hypothesised that delivery of early nutritional support in critically ill patients through the parenteral route is superior to that through the enteral route. They conducted a randomised multicentre trial in 33 English ICUs involving patients with an unplanned admission. Patients could be fed through either the parenteral or the enteral route to a delivery route, with nutritional support initiated within 36 hours after admission and continued for up to five days. The primary outcome was all-cause mortality at 30 days. A total number of 2400 patients were enrolled from which 2388 (99.5%) were included in the analysis (1191 in the parenteral group and 1197 in the enteral group). By 30 days, 33.1% in the parenteral group and 34.2% in the enteral group had died (NS). There were significant reductions in the parenteral group, as

compared with the enteral group, in rates of hypoglycaemia (44 patients [3.7%] vs. 74 patients [6.2%]; $p = 0.006$) and vomiting (100 patients [8.4%] vs. 194 patients [16.2%]; $p < 0.001$). In contrast, there were no significant differences between the parenteral group and the enteral group in the mean number of treated infectious complications (0.22 vs. 0.21; $p = 0.72$), 90-day mortality (37.3% vs. 39.1%, NS), in rates of other secondary outcomes and adverse events. Caloric intake was similar in the two groups, with the target intake not achieved in most patients. The results from this study underline the enteral route as the preferred route to deliver nutrition in critically ill patients. Furthermore, given the fact that most patients did not achieve their caloric goal during the course of the study, one might argue that mild underfeeding or trophic feeding in the first days of ICU stay might not be such a bad thing at all.

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Verkorte productinformatie Mycamine® 50 mg/100 mg (gebaseerd op SmPC van 18 december 2013) **Samenstelling:** Mycamine® 50 mg/100 mg poeder voor oplossing voor infusie (in natriumvorm). De toe te dienen hoeveelheid na reconstitutie is 10 mg/ml en 20 mg/ml, resp. (in natriumvorm). **Farmacotherapeutische groep:** Overige antimycotica voor systemisch gebruik, ATC-code: J02AX05. **Therapeutische indicaties:** Volvassenen, adolescenten ≥ 16 jaar en ouderen: Behandeling van invasieve candidiasis. Behandeling van oesofageale candidiasis bij patiënten voor wie intraveneuze therapie geschikt is. Prophylaxe van *Candida*-infectie bij patiënten die allogene hematopoëtische stamceltransplantatie ondergaan of van wie wordt verwacht dat ze aan neutropenie (absolute neutrofielentelling < 500 cellen/ μ l) gedurende 10 dagen of langer. Kinderen (inclusief neonaten) en adolescenten < 16 jaar: Behandeling van invasieve candidiasis; Prophylaxe van *Candida*-infectie bij patiënten die allogene hematopoëtische stamceltransplantatie ondergaan of van wie wordt verwacht dat ze aan neutropenie lijden (absolute neutrofielentelling < 500 cellen/ μ l) gedurende 10 dagen of langer. Bij de beslisning Mycamine te gebruiken dient rekening gehouden te worden met het potentiële risico voor de ontwikkeling van levertumoren. Mycamine dient daarom uitsluitend te worden gebruikt als andere antifungale middelen niet in aanmerking komen. **Dosering en wijze van toediening:** Behandeling van invasieve candidiasis: 100 mg/dag bij lichaamsgewicht > 40 kg, 2 mg/kg/dag bij een lichaamsgewicht ≤ 40 kg. Als de patiënt in onvoldoende mate reageert, bv. indien de kweken positief blijven of de klinische toestand niet verbetert, dan mag de dosis worden verhoogd tot 200 mg/dag bij patiënten met een lichaamsgewicht > 40 kg of tot 4 mg/kg/dag bij patiënten met een lichaamsgewicht ≤ 40 kg. Behandeling van oesofageale candidiasis: 150 mg/dag lichaamsgewicht > 40 kg, 1 mg/kg/dag bij een lichaamsgewicht ≤ 40 kg. Er zijn onvoldoende gegevens beschikbaar over de farmacokinetiek van micafungine bij patiënten met ernstige leverfunctiestoornis. **Contra-indicaties:** Overgevoeligheid voor het werkzame bestanddeel, voor andere echinocandinen of voor één van de hulpstoffen. Zie de volledige SmPC. **Waarschuwingen en voorzorgen bij gebruik:** **Hepatische effecten:** De ontwikkeling van foci van veranderde hepatocyten (FAH) en hepatocellulaire tumoren werd bij ratten waargenomen na een behandelperiode van 3 maanden of langer. De veronderstelde drempelwaarde voor tumorontwikkeling bij ratten ligt ongeveer in het bereik van de klinische blootstelling. De relevantie van deze bevindingen voor het therapeutisch gebruik bij patiënten kan niet worden uitgesloten. De leverfunctie dient zorgvuldig te worden gecontroleerd tijdens behandeling met micafungine. Om het risico op adaptieve regeneratie en mogelijk daaropvolgende levertumorvorming te minimaliseren, wordt vroegtijdig staken aanbevolen indien significante en persistente verhoging van ALT/AST optreedt. De micafungine behandeling dient uitgesteld te worden na een zorgvuldige bepaling van risico's en voordelen met name bij patiënten met ernstige leverfunctiestoornissen of chronische leverziekten die preneoplastische aandoeningen vertegenwoordigen, zoals gevorderde leverfibrose, cirrose, virale hepatitis, neonatale leverziekte of congenitale enzymdefecten, of bij het tegelijkertijd ondergaan van een behandeling met hepatotoxische en/of genotoxische eigenschappen. Er kunnen anafylactische/anafylactoïde reacties optreden, met inbegrip van shock. Bij het optreden van dergelijke reacties moet infusie van micafungine worden stopgezet en de juiste behandeling worden ingesteld. Exfoliatieve huidreacties zijn gemeld. Als patiënten huiduitslag ontwikkelen dan dienen zij nauwkeurig geobserveerd te worden en dient de behandeling met micafungine gestopt te worden als de laesies verergeren. In zeldzame gevallen is er hemolyse met inbegrip van acute intravasculaire hemolyse of hemolytische anemie gerapporteerd. In dit geval dient nauwlettend te worden gevolgd of er geen verslechtering optreedt en er dient een risico/baten analyse gedaan te worden van voortzetting van de therapie. Micafungine kan nierproblemen, nierfalen en afwijkende nierfunctietests veroorzaken. Patiënten dienen nauwlettend te worden gecontroleerd op verslechtering van de nierfunctie. **Interacties:** Micafungine bezit een gering vermogen tot interactie met geneesmiddelen die via CYP3A-gemedieerde routes worden gemetaboliseerd. Gelijktijdige toediening van micafungine met amfotericine B-desoxycholaat is alleen toegestaan wanneer de voordelen duidelijk opwegen tegen de risico's, met een scherpe controle op mogelijke toxiciteit van amfotericine B-desoxycholaat. Patiënten die Mycamine in combinatie met sirolimus, nifedipine of itraconazol ontvangen, dienen te worden gecontroleerd op toxiciteit van sirolimus, nifedipine of itraconazol. Indien noodzakelijk moet de dosering van deze middelen worden verlaagd. **Bijwerkingen:** De volgende bijwerkingen deden zich vaak voor: leukopenie, neutropenie, anemie, hypokaliëmie, hypomagnesiëmie, hypocalciëmie, hoofdpijn, febriliteit, misselijkheid, braken, diarree, buikpijn, verhoogd bloedkaline-fosfatase, verhoogd aspartaataminotransferase, verhoogd alaneaminotransferase, verhoogd bilirubine in het bloed (inclusief hyperbilirubinemie), afwijkende leverfunctietest, uitslag, pyrexie, koude rillingen. Naast bovengenoemde bijwerkingen zijn bij kinderen tevens vaak trombocytopenie, tachycardie, hypertensie, hypotensie, hyperbilirubinemie, hepatomegalie, acuut nierfalen en verhoogd bloedureum gemeld. Kinderen < 1 jaar toonden ongeveer 2 keer zo vaak een verhoogde ALT, AST en AP dan oudere kinderen. De volgende bijwerkingen kwamen soms voor: pancytopenie, trombocytopenie, eosinofilie, hypoalbuminemie, anafylactische/anafylactoïde reactie, overgevoeligheid, hyperhidrose, hyponatriëmie, hyperkaliëmie, hypofosfatemie, anorexia, slapeloosheid, angst, verwardheid, slapeloosheid, tremor, duizeligheid, dysgeusie, tachycardie, palpities, bradycardie, hypotensie, hypertensie, blozen, dyspnee, dyspepsie, obstipatie, leverinsufficiëntie, verhoogd gamma-glutamyl-transferase, geelzucht, cholestaese, hepatomegalie, hepatitis, urticaria, pruritus, erytheem, bloedcreatinine verhoogd, bloedureum verhoogd, verergerde nierrinsufficiëntie, trombose op injectieplaats, infuusplaats ontsteking, injectieplaats pijn, perifeer oedeem, verhoogde bloedalactaatdehydrogenase. De volgende bijwerkingen kwamen zelden voor: hemolytische anemie en hemolyse. Van de volgende bijwerkingen kan de frequentie niet worden bepaald: gedissimineerde intravasculaire stolling, shock, hepatocellulaire schade inclusief gevallen met dodelijke afloop, toxische huida eruptie, erythema multiforme, het syndroom van Stevens-Johnson, toxische epidermale necrolyse, nierfunctie-stoornissen, acuut nierfalen. **Afleverstatus:** UR. **Overige productinformatie:** Astellas Pharma B.V. Sylviusweg 62, 2333 BE Leiden. Tel.: 071-5455854 Fax: 071-5455850.

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