COMMENTARY

Selective digestive decontamination: for everyone, everywhere?

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Nosocomial infections thrive in intensive care units (ICUs),[1-3] with nosocomial pneumonia being the most common. Often, the source of infection is endogenous,[4] with a positive relation between the development of nosocomial pneumonia and colonisation of the digestive tract and the oropharynx.[5] Stoutenbeek et al[6] first attempted to prevent nosocomial pneumonia with antimicrobial agents. They aimed to reduce gastrointestinal colonisation by pathogenic microorganisms in patients with multiple trauma, an approach known as selective digestive decontamination (SDD)—"selective" because potentially pathogenic organisms are targeted while the normal anaerobic flora are not. SDD regimens generally consist of topical oropharyngeal administration of non-absorbed antimicrobials (usually polymyxin B, tobramycin, and amphotericin B) that are active against most gram-negative bacteria and fungi, combined, for the first 3–4 days, with systemic antimicrobials, including a broad-spectrum antibiotic (usually cefotaxime).

Many studies have compared the potential value of SDD as an intervention to prevent infection with the potential risks associated with the use of the antibiotics, especially antimicrobial resistance. Although early meta-analyses only showed reduced occurrence of nosocomial infection,[7,8] more recent meta-analyses have shown improved survival rates in ICU populations.[9–11] There are several problems with the interpretation of clinical trials of SDD. First, the link between nosocomial pneumonia and mortality, the attributable mortality, is still uncertain. Nosocomial pneumonia may itself cause increased mortality, but may be more likely to develop in sicker patients with inherently higher mortality rates. If so, reducing the occurrence of nosocomial infection would not necessarily be expected to reduce mortality. Second, the criteria used to define nosocomial pneumonia are controversial, with some studies relying on clinical and radiological findings and others on microbiological specimens. Differing criteria may largely account for the variable occurrence of ventilator-associated pneumonia—from 5%–85%—in control groups of studies assessing SDD.[12] Third, there is no single SDD regimen. Most studies include various systemic agents, but others use only topical administration.[12] Some argue that there is a benefit on mortality only with the combined approach, because of the inclusion of the systemic drug.[13] However, the reverse has also been claimed; Bergmans et al[14] found that topical administration alone, aimed at preventing oropharyngeal colonisation without influencing gut colonisation, could reduce the occurrence of ventilator-associated pneumonia. Fourth, the specific population of patients can influence results; trauma and surgical patients, less colonised at the outset, are more likely to benefit than medical patients.[11] These various elements may partly account for the observation that the benefit of SDD may be inversely related to the quality of the trial.[10]

Several studies have shown increased infections due to resistant staphylococci and enterococci in patients receiving SDD.[15-19] Oral vancomycin can encourage growth of vancomycin-resistant enterococci and vancomycin-intermediate *Staphylococcus aureus*.[18,19] The use of third-generation cephalosporins may promote the development of gram-negative organisms, such as *Pseudomonas* and *Acinetobacter* spp, and those harbouring extended-spectrum β-lactamases, such as *Klebsiella* or *Enterobacter spp*.[20] The patterns of resistance created may be complex: Sanchez Garcia et al[18] found a reduction in the occurrence of infection with Gram-negative organisms from 47·4% to 13·0 %, but the colonisation with resistant gram-positive organisms (staphylococcus, enterococci) increased significantly. This study suggested that SDD was a cost-effective intervention; length of stay decreased from 16·5 to 11 days, and cost per ICU survivor was reduced from US$16 300 to $12 000. However, the clinical benefit may be outweighed by the burden of microbial resistance in the future.

In this issue of *The Lancet*, Evert de Jonge and colleagues assessed the effects of SDD in an intensive care population. They compared two separate units in the same centre. They used a standard regimen, with a combination of topical and systemic antibiotics. The only deviations from standard was nebulised polymyxin E or amphotericin B in patients with sputum cultures positive for gram-negative bacteria or yeasts, and of amphotericin B, polymyxin E and tobramycin suppositories in patients with blind bowel-loops. The results are important for several reasons. First, the investigators showed a substantial reduction in mortality (24 % *vs* 31%) and a shorter length of ICU stay (6·8 *vs* 8·5 days) in patients given SDD. Second, they showed no increased bacterial resistance, despite a follow-up of more than 2 years, which included cultures of the ICU environment. Furthermore, there was a reduction in the occurrence of ceftazidime-resistant enterobacteriaceae in the unit where SDD was used. Third, there were lower overall antibiotic costs in the SDD group than in the control patients. Fourth, there was no difference in outcome between surgical and medical patients.

So should SDD be applied routinely in all ICUs? To the question does SDD work, the answer now must definitely be yes—SDD reduces mortality. But, do the data apply to all environments? Despite the results in de Jonge's study from the Netherlands, the risks of bacterial resistance remain. Whether to use SDD or not will depend on the risk of resistant organisms in a given environment, and the population of patients. So, in ICUs in an area with a high incidence of vancomycin-resistant enterococci or meticillin-resistant *S aureus*, SDD may not be appropriate, and in general, surgical and trauma patients will benefit more than medical patients who enter the ICU already colonised.[21] Whatever individual units decide, regular surveillance samples must be taken to monitor the long-term effects of this intervention.

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Ischaemic tolerance: a window to endogenous neuroprotection?

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Global or focal sublethal cerebral ischaemia for a few minutes confers transient tolerance to a subsequent more severe and sustained ischaemic event. This phenomenon, called ischaemic tolerance, has been demonstrated in animal models of cerebral ischaemia, and in other diseases of the central nervous system,[1,2] and can be observed in human beings with different conditions of reduced cerebral blood flow.[3,4] Ischaemic tolerance seems to be a fundamental non-specific cellular response, because its signals, transducers, and effectors have also been seen in hypoxia-tolerant or hibernating animals.[5] Because ischaemic tolerance can confer endogenous neuroprotection, the underlying molecular mechanisms of tolerance induction have been studied extensively in animal models and in cell culture.[1–3,6–8] From this knowledge, cerebral ischaemic tolerance can be subdivided into at least two temporal profiles: a "classical" rapid form, in which the trigger induces neuroprotection within minutes; and a "delayed" form, in which the protected cellular state develops over hours or days and usually involves de-novo protein synthesis.[1]

The underlying pathophysiology of ischaemic tolerance is poorly understood. A stimulus leading to ischaemic tolerance is probably followed by functional impairment, but not by brain-tissue damage, and the induced molecular mechanisms can be categorised into two subgroups.[1] First, a cellular defence against ischaemia induced in neurons by post-translational modification of proteins and/or by the expression of new proteins via signalling to the nucleus. This signalling cascade may strengthen the influence of cellular protection or may inhibit apoptosis. Second, a cellular stress response involving de-novo synthesis of stress proteins that may lead to an increased capacity for intracellular protection. These proteins serve as cellular "chaperones" by unfolding and helping to dispose of denatured proteins. In this issue of *The Lancet*, Mary Stenzel-Poore and colleagues show the importance of this processing of unfolded proteins in whether neurons survive.

Because ischaemic tissue damage is the result of a complex pathophysiological cascade compromising many molecular events, not only substrate restriction but also noxious events can induce ischaemic tolerance. Thus different triggers, including global or focal transient cerebral ischaemia, hyperbaric oxygenation, inflammation, seizure activity, cortical spreading, depression, metabolic inhibition, oxygen-free radicals, hypothermia or hyperthermia, and cerebellar stimulation, induce ischaemic tolerance.[2] Most of these endogenous or exogenous stressors induce both rapid and delayed ischaemic tolerance. However, because many diseases of the central nervous system share common cell-death pathways, one stressor can induce tolerance against another (cross-tolerance).[2] Thus triggers inducing ischaemic tolerance are not necessarily specific for ischaemia and, because of stereotypical molecular responses of cells to damage, the same stressors that elicit ischaemic tolerance in brain may elicit tolerance in other organs. Induction and mechanisms of ischaemic tolerance in different organs have similar features.[2] In fact induction of tolerance in one organ may spread via the peripheral nervous system or paracrine mechanism to other organs (remote preconditioning). The further identification and characterisation of preconditioning stimuli that are effective but relatively benign is of utmost importance to translate the endogenous ischaemic tolerance into a tool for therapeutic options.

Stenzel-Poore and colleagues describe different possible target genes that are involved in upstream signalling pathways of ischaemic tolerance and in the activation of co-ordinately expressed genes. They also identify different subgroups of "tolerance" genes that are triggered in a complex pattern of gene expression by ischaemic preconditioning and which respond in a coordinated manner to counteract the cellular ischaemic death-cascade.

However, models of ischaemic tolerance have been developed that use clinically approved drugs (erythropoietin,[6] isoflurane,[7] ATP-sensitive potassium-ion channel-openers[8]) as inducing effectors. If a multifaceted and coordinated programme involving the expression of multiple genes in neurons, glia, and endothelial cells guides ischaemic tolerance, it seems unlikely that such a complex