

# Gut overgrowth harms the critically ill patient requiring treatment on the intensive care unit

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## ABSTRACT

Overgrowth is defined as  $\geq 10^5$  potential pathogens per ml of saliva and/or per g of faeces. There are six 'normal' potential pathogens carried by healthy individuals and nine 'abnormal' potential pathogens carried by individuals with underlying disease both chronic and acute. Surveillance cultures of throat and/or rectum are required to identify overgrowth of 'normal' and/or 'abnormal' potential pathogens. There is a qualitative and quantitative relationship between surveillance samples and diagnostic samples of tracheal aspirate and blood, i.e., as soon as potential pathogens reach overgrowth concentrations in the surveillance samples, the diagnostic samples become positive for identical potential pathogens. Digestive tract decontamination aims at the eradication of overgrowth in order to prevent severe infections of lower airways and blood. Parenteral cefotaxime controls overgrowth of 'normal' bacteria, and enteral polyenes control overgrowth of 'normal' *Candida* species. Enteral polymyxin and tobramycin (with or without) vancomycin control 'abnormal' overgrowth.

**Key words:** overgrowth, 'normal' potential pathogens, 'abnormal' potential pathogens, surveillance samples, diagnostic samples, selective digestive decontamination (SDD)

## Surveillance cultures required to identify overgrowth

Traditionally, infection control on the intensive care unit (ICU) includes: (1)

- i. Obtaining diagnostic cultures to confirm the clinical diagnosis of infection;
- ii. Parenteral antimicrobials administered only after an infection was diagnosed;
- iii. Five infection control manoeuvres with the endpoint of control of transmission of potential pathogens via the hands of healthcare workers (HCW): hand disinfection, isolation, personal protective equipment (glo-

ves, gowns and aprons), care of patients' equipment and environment.

These guidelines are based on the concepts that transmission invariably leads to infections and that prophylactic antimicrobials are associated with antimicrobial resistance.

In 1978, Chris Stoutenbeek, intensivist and clinical researcher on a trauma ICU in Groningen, The Netherlands came to the conclusion that the traditional policy of infection control on ICU does

not work. (2) The majority of his trauma patients were still inflamed, the severe infection rate was still high, mortality was approximately 30%, and resistance invariably emerged so that he had to change his parenteral antimicrobial policy approximately every two years.

That year in Firenze (Italy) he met and discussed the infection problem on his trauma ICU with Steven Schimpff, who wrote one of the first papers on infection in trauma patients. (3) Steven Schimpff convinced Chris Stoutenbeek that only the introduction of surveillance samples of throat and rectum may allow a better insight into the infection problem in trauma patients, (4) for the simple reason that surveillance cultures, allow the detection of overgrowth of potential pathogens both normal and abnormal, and, hence, the distinction between endogenous (primary and secondary) and exogenous infections. These three terms are based upon the pathogenesis of the infections in order to determine a prophylactic protocol.

Chris Stoutenbeek designed a prospective study to be conducted over two years (1979-1980) involving the use of both diagnostic and surveillance samples from severely traumatised patients requiring ventilation for at least five days. He used the following definitions. Normal flora is carried by healthy individuals (i.e., trauma patients before ICU admission): *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* in the oropharynx, *Escherichia coli* in the gut and *Staphylococcus aureus* and *Candida albicans* in throat and gut. Abnormal flora includes nine bacteria carried in throat and gut by individuals with chronic and acute diseases (after ICU admission). There are eight aerobic Gram-negative bacilli (AGNB): *Klebsiella*, *Enterobacter*, *Citrobacter*, *Proteus*, *Morganella*, *Serratia*, *Acinetobacter* and *Pseudomonas* species. (5) Methicillin-resistant *Staphylococcus aureus* (MRSA) is also abnormal. (6)

A primary endogenous infection is an infection caused by 'normal' and 'abnormal' potential pathogens present in the admission flora. A secondary endogenous infection is caused by

'abnormal' bacteria not present in the admission flora but acquired later and carried during treatment on the ICU. An exogenous infection is an infection caused by 'abnormal' bacteria not carried at all in throat and/or gut. Gut overgrowth is defined as  $\geq 10^5$  potential pathogens per ml of digestive tract secretion (saliva and/or faeces). (7)

Fifty-nine patients were enrolled in this landmark epidemiological study. (8) The infection rate was 81%, with 48 patients developing 94 infection episodes, 35 of which were lower airway infections. 37% and 28% of the severely traumatised patients carried abnormal flora in throat and gut on admission, respectively. Amongst the lower airway infections, 75% were primary endogenous, 20% were secondary endogenous and 5% were exogenous. Most of the primary endogenous lower airway infections were due to the normal respiratory pathogens *S.pneumoniae*, *H.influenzae* and *S.aureus*. *Pseudomonas aeruginosa*, *Klebsiella*, *Proteus* and *Enterobacter* species were the predominant abnormal AGNB causing secondary endogenous lower airway infections. Identical potential pathogens were present in the throat swabs invariably in overgrowth concentrations. *Acinetobacter* and *Pseudomonas* species caused exogenous lower airway infections. Five (8%) trauma patients died. Resistance did not occur as the study lasted only two years.

Stoutenbeek's study was the first ICU study providing qualitative and quantitative data for both surveillance and diagnostic cultures. After analysis Stoutenbeek concluded that there is a qualitative and quantitative relationship between surveillance and diagnostic samples. As soon as potential pathogens reach overgrowth concentrations in the surveillance samples, the diagnostic samples become positive for identical potential pathogens. (9)

### **Digestive tract decontamination aims at the eradication of overgrowth**

Decontaminating agents are antimicro-

bials that are able to eradicate if already present, and prevent overgrowth of both 'normal' and 'abnormal' flora. Decontaminating agents include parenteral antimicrobials that are excreted via saliva and bile in high concentrations in throat and/or gut and non-absorbable enteral antimicrobials.

At the beginning of the 1980's, Stoutenbeek, in designing the selective digestive decontamination (SDD) protocol, searched for a parenteral antimicrobial with adequate spectrum and pharmacokinetic properties to be included in a prophylaxis for critically ill patients requiring treatment on ICU. Cefotaxime was chosen because:

Its spectrum included both 'normal' and most 'abnormal' bacteria: (10)

Its pharmacokinetic properties included a high level of excretion in saliva and bile, associated with eradication of overgrowth. (11) Salivary and biliary samples were obtained from adult patients requiring biliary surgery and receiving 1g of cefotaxime intravenously four times daily. High concentrations were measured: 6mg/L of saliva and 20mg/L of bile (table 1).

Enteral polyenes nystatin (12) and amphotericin B (13) aim at the control of fungal overgrowth. The combination of polymyxin E (14) and tobramycin (15) control 'abnormal' overgrowth, whilst enteral vancomycin targets overgrowth due to 'abnormal' MRSA. (16)

Sixty-three patients received SDD using parenteral cefotaxime and enteral amphotericin B, polymyxin E and tobramycin. (8) Emphasis was laid on the oropharyngeal decontamination, using a sticky paste mixed with 2% of amphotericin B, polymyxin E and tobramycin. Oropharyngeal overgrowth was abolished within 3 days. Rectal overgrowth decreased significantly after 5 days. The successful control of overgrowth (17) resulted in a significant reduction of colonisation and infection of the normally sterile lower airways and internal organs. The total infection rate decreased to 16%.

Twenty-five years ago, Chris Stoutenbeek examined the relationship between oropharyngeal overgrowth and lower airway infections following

**Table 1. Antimicrobials selected for SDD to control overgrowth.**

Antimicrobials selected for SDD	Concentrations (mg/L) in		
	Saliva	Bile	Faeces
Cefotaxime	6	20	
Amphotericin B			60
or nystatin			<100
Polymyxin E			16 – 1,000
Tobramycin			100
Vancomycin			3,000 – 24,000

SDD, selective digestive decontamination.

migration. More recently, our group analysed the relationship between gut overgrowth and bloodstream infections as a consequence of transmural migration or translocation. (18) We found a similar qualitative and quantitative relationship in that SDD including the enteral antimicrobials reduces bacteraemia due to eradication of gut overgrowth.

### Mechanism of action of digestive tract decontamination

There is still some ambiguity of how SDD achieves its significant benefits. Rather than selectively removing aerobic bacteria and leaving the anaerobic intestinal microbes unaffected as the name misleadingly implies,

SDD actually works by achieving high antimicrobial concentrations effective against overgrowth of both normal and abnormal flora. (19) Despite the 64 RCTs and 11 meta-analyses assessing SDD, this ambiguity over its mechanism of action still exists and to which we have unfortunately contributed by continuing to use the term SDD. It is a contradiction in terms to be selective and yet achieve effective decontamination or eradication of aerobic overgrowth. To achieve selective eradication of aerobic overgrowth would lower the rate of molecular oxygen consumption permitting an increase in pO<sub>2</sub> of the gut lumen content from 5mmHg to 60mmHg; (20) under such conditions strictly anaerobic micro-organisms can no longer survive even though they may not themselves be sensitive to the decontaminating agents.

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