# A Clinician's View of Engineering and Technology in Intensive Care - Model-based Therapeutics and Patient Outcomes

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**Abstract:** This paper presents a summary of previous and current research at the Christchurch Hospital Intensive Care Unit from the point of view of an intensive care specialist who has worked in the field for the past 18 years. All the major areas of sedation-agitation, cardiovascular and mechanical ventilation management, glucose control and sepsis diagnosis are covered as case studies, including model developments and clinical outcomes. The overall approach is described as "Model-based Therapeutics" and has the philosophy of a "one method fits all" rather than the more typical "one size fits all" approach. The research presented shows the way forward to next generation health care, where current medical equipment, sensors and drugs are used in a smarter way to develop patient-specific diagnosis and therapy.

*Keywords:* Intensive Care Unit; model-based therapeutics; clinician; engineering and computation; agitation-sedation; cardiovascular and lung ventilation management; glucose control; sepsis diagnosis

## 1. INTRODUCTION

Intensive care is one of the most challenging areas of modern medicine. With aging populations and increased complexity of care, the social and economic burden of intensive care is increasing, and accounts for 10%, or more, of all healthcare costs, or 1-1.5% of GDP in western countries. Economically, these costs are beginning to bring some healthcare systems to their knees.

It is also a technology laden area of medicine, with mechanical ventilators, semi-automated infusion pumps, and a wide range of sensors. However, while the technology used continues to evolve and improve incrementally, it has not changed radically in 30 years. Thus, improving patient outcomes, while restraining cost, in the intensive care unit (ICU) of the next 10 years, will revolve around how we use that technology and maximize its potential

Importantly, the technology and how clinical staff interpret the information it provides, have not improved patient outcomes or productivity in care while the main cost of intensive care is in clinical staff. Thus, while technology, particularly computers, has driven productivity revolutions in many industries, including parts of medicine, it has failed to do so in the ICU. This paper examines the means by which this issue can be addressed, and how there is a need to develop technologies that overcome these obstacles.

In a typical intensive care there is very little time to diagnose a patient's condition and determine the proper treatment. Patient's lives ultimately can depend on clinical staff doing the right thing at the right time. In addition, while patients are continually monitored, they are only infrequently examined or diagnosed, and at set points in time. Thus, a great deal of potentially valuable information is lost, and the variability that defines the critically ill patient can wreak extensive havoc. What is needed is the ability to accurately and continuously inform bedside clinical staff of what is really going on with their patient – something that modern technologies and physiological knowledge can do in combination. Thus, it's an area which creative and adaptive solutions using engineering and computational methods, mixed with clinical and physiological knowledge, can save lives, time and cost.

The Department of Intensive Care in Christchurch, New Zealand has seen the development of highly innovative health care initiatives including glucose control, cardiovascular and ventilation management, agitation sensing and optimal sedation and real-time sepsis diagnostics (Blakemore et al 2008, Chase et al 2008, Chase et al 2007, Lonergan 2006a, Lonergan 2006b, Hann et al 2005a, Hann et al 2008, LeCompte et al 2009, Shaw et al 2007,Smith et al 2004, Hann et al 2005b, Starfinger et al 2008, Starfinger et al 2007, Sundaresan et al 2009, Chase et al 2004, Shaw et al 2003, Chase et al 2004, Becouze et al 2007). The glucose control protocol developed has lead to a clinical practice change with significant savings on mortality, cost and overall patient outcome (Chase et al 2008).

The overall approach is referred to as model-based therapeutics or MBT (Chase et al 2007, Lonergan 2006a, Lonergan 2006b, Hann et al 2008). The philosophy is to develop a "one-method-fits all" rather than static or fixed 'one-size-fits all' approaches that predominate in results in randomised clinical trials (RCTs). RCTs produce outcomes

of risk based on treatments given. Thus, when this evidence is translated into clinical practice, patients can only be treated for the risk of a particular disease or condition. The result: treatments are given blindly for an indefinite period of time for diseases or conditions that often don't exist. Thus, the "evidence" gained from RCTs can not be used to predict outcomes of treatments titrated to patient-specific responses.

The goal of MBT is to develop patient-specific diagnoses and therapies that make more effective use of existing sensors and technologies.

The common approach in intensive care to patient management is to 'cover all bases' which typically leads to over prescribing of therapies. For example, patients tend to be over-feed, over-sedated, kept on mechanical ventilation for too long, and given far more drugs (e.g. antibiotics and inotropes) than is necessary. Hence, significant costs can be incurred without benefitting patients (Mullner et al 2004).

The primary problem is that the measurements and patient responses to various therapies given are very complex, even for highly trained specialists, who have to make a best "guess" at what is going on. Hence, this process is often 'hit and miss' and takes time (and error) to get right. For sicker patients who are less tolerant of incorrect treatments, there may be little time to make a correct diagnosis. It is often impossible to know, exactly, the real causes of the particular physiological dysfunction. For example there can be several different conditions affecting the circulation that look the same on the intensive care monitors.

Doctors are helped by using other diagnostic tools, such as cardiac echocardiography, lab tests and computerized tomography (CT) scans. However, these measurements are not available immediately at the bedside, and they require expert technical skills and interpretation, and thus add cost. Finally, no intermittent diagnostic test can truly tell the nurse or doctor what is going on physiologically as it happens (in real-time).

What is required are methods to turn a range of numbers and sensor outcomes into a clear and well-understood physiological picture of patient condition. This approach takes best advantage of the available technology to translate physiological and clinical knowledge in textbooks and research, directly to the bedside in a way that thus best matches clinical training and knowledge. From this outcome, we can create improved productivity in care.

## 2. CASE STUDIES

### 2.1 Agitation/sedation:

Sedative delivery in intensive care is fundamental to effective agitation management and is the basis for providing comfort and relief to the critically ill. The yearly cost in the US of sedatives and analgesics in the ICU was estimated to be $0.8-1.2B US in 2001 (Fraser and Riker, 2001).

A landmark study (Kress et al, 2000) of sedation interruption showed significant reductions in the time spent on mechanical ventilation and the length of stay. Another study (Girard et al, 2008) has shown that sedative interruption in combination with successful spontaneous breathing trials resulted in earlier discharges and increased 12 month survival. A recent review concludes that systematic interventions to improve sedation practice and maintain patients at an optimal sedation level in the ICU may improve patient outcomes and optimize resource usage (Jackson, et al 2010). However, when sedation is switched off when patients are not ready to be removed from mechanical ventilatory support, this resulted in an mortality de Wit et al, 2008. This demonstrates the dangers of simply reducing sedation in a simple protocol without proper knowledge of the underlying dynamics. In other words, it's not what drug or what dose that's given, it's how it's delivered.

Specifically, an objective, physiologically-based, agitation scale, models or understanding of agitation-sedation dynamics, and effective, well-understood infusion protocols are needed Prior research has developed and clinically validated an agitation index (Chase et al 2004) with further refinements to include detection of grimacing and quantification (Becouze et al 2007). Agitation-Sedation Dynamic models have also been developed based on clinical data (Chase et al 2004) and have shown significant potential for the development of improved protocols (Rudge, et al 2005). This approach allows patient-specific drug delivery and should be the focus of new research.

### 2.2 Model-based cardiac diagnosis and therapy:

The approach to cardiovascular management in critical care commonly involves titrating drugs and giving fluids based mainly on arterial pressure but with some other measurements including central venous pressure, ECG and $SPO_2$ waveforms. The interpretation of this diverse and rather limited data set is very difficult and thus clinical staff primarily rely on experience and intuition to make a diagnosis or administer a treatment.

For example, the main reason for giving inotropes is to improve cardiac muscle function. Hence, to see the real physiological effect of inotropes requires analysis of left ventricular pressure-volume (PV) loops, which has been well studied in the literature (Guyton 2000). Yet, even though registrars and nurses get exposed to PV loops from in their training, this concept is often completely lost when they reach clinical practice. A recent (unpublished) data audit has shown that even with arterial pressure essentially clamped, the left ventricular power index, which assesses the power of the heart to pump blood (the key outcome metric) can vary significantly, as shown in Figure 1.

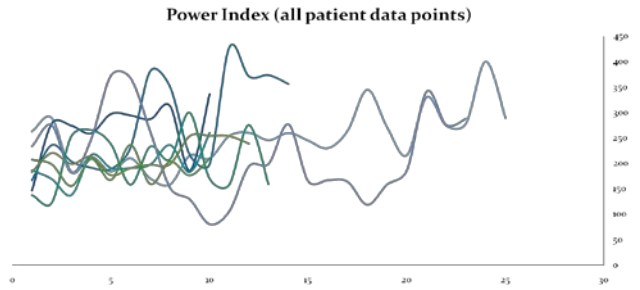


Figure 1: Plot of power index with MAP essentially clamped.

Therefore, there is an urgent need for a more physiological representation of the data displayed on intensive care monitors which could be achieved by an appropriate patient specific cardiovascular model. Previous work (e.g. Starfinger et al 2008, Starfinger et al 2007), has developed and validated a lumped parameter cardiac model on animal models. This success has led to the development of clinical trials. More specifically, animal studies have already shown the ability to:

- Diagnose pulmonary embolism (PE) (Starfinger et al 2007)
- Diagnose septic shock (Starfinger et al 2008a)
- Capture the impact of hypovolemia (Starfinger et al 2008a)
- Capture the impact PEEP on circulation (Starfinger et al 2008b)
- Capture the affect of adrenaline and inotropes on circulation to optimise titration (Chase et al 2010)

These results cover many common diagnostic difficulties and therapeutic interactions. They are also have unique capabilities. Importantly, the ability to clearly define, in a physiological sense, these issues can dramatically improve diagnosis, therapy selection and care in intensive care. In particular, because cardiovascular dysfunction is a leading cause of ICU mortality, these tools can have immediate impact.

## 2.3 Management of Mechanical Ventilation (MV):

Acute Respiratory Dysfunction Syndrome (ARDS) is a major cause of hospitalization with mortality rates from 30-70% Bersten et al (2002). Despite many recent studies on MV treatment there are no well established methods to determine an optimal, patient-specific positive end expiratory pressure (PEEP), a critical MV setting, or any other ventilator settings. The objective of this research is to develop a simple model that can be run at the bedside with minimal intervention to optimise PEEP and MV therapy.

Clinical trials are currently in progress, to validate the model's ability to predict the outcome of a change in PEEP on the recruitment of lung units or alveoli. Further, as seen in Figure 2, the model can assess the impact of PEEP on net recruitment (Sundaresan et al 2009), which is a primary physiological and clinical end-point or goal.

MV is used to improve recruitment of lung units to aid recovery, while minimising excessive tidal volumes and/or pressures that can lead to ventilator induced lung injury (VILI) of healthy units. Hence, the goal is to use PEEP to prevent derecruitment of lung units at end expiration (preventing their collapse and associated damage due to continued recruitment and derecruitment). Hence, the ability to noninvasively capture net recruitment at any PEEP without the need for other technologies, and to do so at any time, will provide significant insight to clinical management of MV.

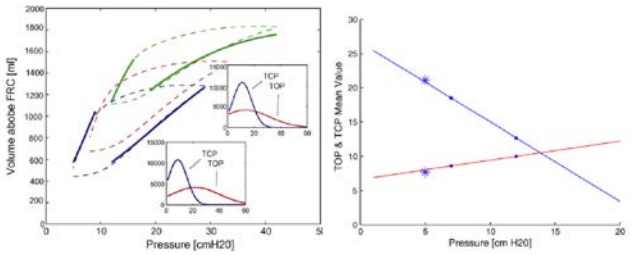


Figure 2: Example patient fit and prediction (left) and volume responsiveness of inspiratory (lower) and expiratory (upper) limbs. Asterisk indicates predicted values, lines show the linear trend prediction.

Figure 3 shows this model in action on an initial clinical trial. The figure shows net increase in recruitment for an intensive care patient as a function of PEEP. It is clear that a PEEP of 20cm$H_2O$ is the point at which net recruitment is maximised and thus an optimal, physiologically and clinically relevant PEEP value. Importantly, the initial clinical setting for this trial was a PEEP of 10cm$H_2O$, a much lower value that had not been changed in some time, while the patient condition had evolved, illustrating a further advantage in that such a patient-specific, model-based method can be used frequently to evaluate and track patient condition.

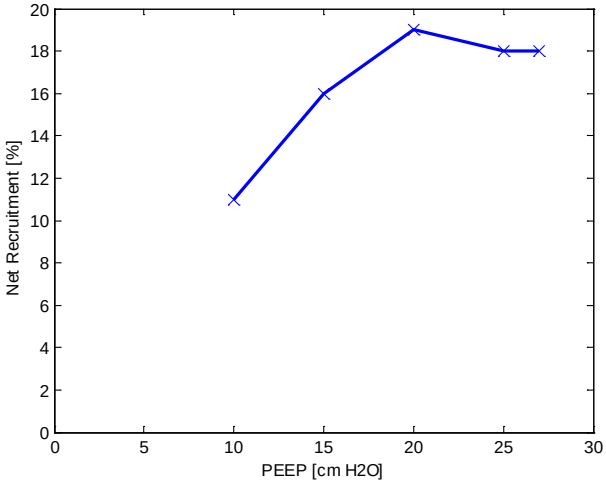


Figure 3: Net recruitment as a function of PEEP for an ICU patient.

It is clear from Figure 3 that one would clinically never add PEEP past a point where net increase in recruitment did not change, as it risks VILI, as well as depressing venous return and cardiac output for no gain (or potential loss) in lung function through increased dead space. Thus, the model can provide clear, physiologically and clinically relevant insight that is currently completely blind to the clinical staff managing MV.

### 2.4 Glucose control and sepsis diagnosis

Hyperglycemia is prevalent in critical care, and leads to increased risk of myocardial infarction, organ failure, infection and death. The hyperglycemic critically ill patient is also highly dynamic, with excessive, highly variable insulin resistance due to their condition. Tight glycemic control (TGC) can reduce mortality if blood glucose can be kept in a target range consistently.

Several studies have reduced mortality up to 40% in patients who stay 3-5 days or longer in the ICU (Chase et al 2008, Van den Berghe et al 2006, Krinsley 2004). However, several other studies have failed to replicate these results (NICE-SUGAR study 2009). The difficulty of providing real-time, adaptive and patient-specific TGC that is effective has prevented this therapy from being widely used.

In particular, most protocols are fixed and static, focusing on insulin dosing in response to blood glucose levels (Chase et al 2006). These protocols thus completely fail to address patient-specific and time varying insulin resistance. Thus, what works well for some patients can fail completely for others. This difficulty is a perfect example of the difference between one size fits all, static approaches to care, and the need for adaptive patient specific therapy.

The Christchurch ICU currently uses a model-derived, adaptive and patient-specific system called SPRINT that has reduced mortality 20-40% for patients staying 3-5 days or longer (Chase et al 2008). The system was derived from metabolic system models validated in a wide range of clinical studies in this ICU, and designed specifically for TGC (Chase et al 2007). It thus directly titrates not off blood glucose level but off patient-specific insulin sensitivity, as derived from the nutrition and insulin interventions and resulting blood glucose response.

Equally importantly, the control has been tight enough to significantly reduce sepsis and infection. In addition, recent studies have shown that it significantly reduced the number, severity and rate of organ failure in patients using SPRINT versus a retrospective, matched cohort, indicating that this reduction provided the foundation for improved mortality. Finally, reduced organ failure resulted in reduced costs, and SPRINT has a net cost savings per patient treated of NZ$1052. Surveys showed that net clinical burden also decreased. Thus, SPRINT provides better outcomes and reduced cost, through a model-derived system, illustrating the power of MBT.

Further improvements, including the use of model-based control are forthcoming to provide further savings and productivity gains. In particular stochastic models of patient variability can be used to provide guaranteed levels of safety from hypoglycaemia (LeCompte et al 2009). This stochastic targeted (STAR) TGC is currently already in use in the Christchurch Womens Hospital Neonatal ICU (LeCompte et al 2009). These models and systems provide direct physiological picture and assessment of the patient's real-time metabolic status, making the optimisation of insulin therapy clearer, more efficient for staff, and more effective for the patient.

Finally, as a glimpse of the future potential of MBT in ICU, these clear physiological pictures of insulin resistance status can be used in other diagnostics. Specifically, patients with sepsis exhibit significantly reduced and variable insulin sensitivity. Thus, this model-based metric, along with other readily available clinical metrics can be used to provide a real-time diagnosis of sepsis (Blakemore et al 2008). In particular, where new sepsis develops in critically ill patients, this task can be highly challenging to distinguish other non-septic causes of inflammation. Hence, the clear physiological picture created of metabolic status can be used to improve other areas of care.

## 6. CONCLUSIONS

The Christchurch Department of Intensive Care has developed a unique clinical-engineering collaboration with the Department of Mechanical Engineering at the University of Canterbury. This collaboration is highly multi-disciplinary, and has led to the development of clinically validated models of each individual major physiological system for diagnosis and decision support. Clinical outcomes and significant cost savings have already been achieved, and clinical trials are in progress in every major area of the ICU. Hence, there is significant potential to link all the main diagnostic and therapeutic methods. The vision for the future is a fully unified, model-based therapeutics system which integrates all drug delivery devices and sensors and provides significantly improved health care at no extra measurable added cost.

## REFERENCES


Blakemore A, Wang SH, Le Compte A, G MS, Wong XW, Lin J, Lotz T, C EH, Chase JG: Model-based insulin sensitivity as a sepsis diagnostic in critical care. Journal of diabetes science and technology 2008, 2(3):468-477.

Chase JG, Shaw GM, LeCompte A, Lonergan T, Willacy M, Wong XW, Lin J, Lotz T, Lee DS, Hann CE: Implementation and Evaluation of the SPRINT Protocol for Tight Glycaemic Control in Critically Ill Patients: A Clinical Practice Change. Critical Care 2008, 12:R49.

Chase JG, Shaw GM, Lotz T, LeCompte A, Wong J, Lin J, Lonergan T, Willacy M, Hann CE: Model-based insulin

and nutrition administration for tight glycaemic control in critical care. Curr Drug Deliv 2007, 4(4):283-296.

Lonergan T, Compte AL, Willacy M, Chase JG, Shaw GM, Hann CE, Lotz T, Lin J, Wong XW: A pilot study of the SPRINT protocol for tight glycemic control in critically Ill patients. Diabetes Technol Ther 2006, 8(4):449-462.

Lonergan T, LeCompte A, Willacy M, Chase JG, Shaw GM, Wong XW, Lotz T, Lin J, Hann CE: A Simple Insulin-Nutrition Protocol for Tight Glycemic Control in Critical Illness: Development and Protocol Comparison. Diabetes Technol Ther 2006, 8(2):191-206.

Hann CE, Chase JG, Lin J, Lotz T, Doran CV, Shaw GM: Integral-based parameter identification for long-term dynamic verification of a glucose-insulin system model. Comput Methods Programs Biomed 2005, 77(3):259-270

Hann, CE, Chase, JG, Ypma, MF, Elfring J, MohdNor, NH, Lawrence P and Shaw GM (2008). "The Impact of Parameter Identification Methods on Drug Therapy Control in an Intensive Care Unit," The Open Medical Informatics Journal, Vol 2, pp 92-104.

LeCompte AJ, Chase JG, Lynn A, Hann CE, Shaw GM, Wong XW, Lin J: Blood Glucose Controller for Neonatal Intensive Care: Virtual trials development and 1st clinical trials. Journal of Diabetes Science and Technology (JoDST) 2009, 3(4):1066-1081

Shaw GM, Chase JG, Starfinger C, Smith BW, Hann CE, Desaive T, Ghuysen A: Modelling the cardiovascular system. Crit Care Resusc 2007, 9(3):263-269.

Smith BW, Chase JG, Nokes RI, Shaw GM, Wake G: Minimal haemodynamic system model including ventricular interaction and valve dynamics. Medical Engineering & Physics 2004, 26(2):131-139

Hann CE, Chase JG, Shaw GM: Efficient implementation of non-linear valve law and ventricular interaction dynamics in the minimal cardiac model. Comput Methods Programs Biomed 2005, 80(1):65--74.

Starfinger et al 2008a: Starfinger C, Chase JG, Hann CE, Shaw GM, Lambermont B, Ghuysen A, Kolh P, Dauby P, Desaive T: Model-based identification and diagnosis of a porcine model of induced endotoxic shock with hemofiltration. Math Biosci 2008, 216(2):132-139.

Starfinger C, Hann CE, Chase JG, Desaive T, Ghuysen A, Shaw GM: Model-based cardiac diagnosis of pulmonary embolism. Comput Methods Programs Biomed 2007, 87(1):46--60.

Sundaresan A, Yuta T, Hann CE, Chase JG, Shaw GM: A Minimal Model of Lung Mechanics and Model based Markers for Optimizing Ventilator Treatment in ARDS Patients. Comput Methods Programs Biomed 2009, 95(2):166-180.

Chase, J G, Rudge, A D, Shaw, G M, Wake, G C, Lee, D, Hudson, I and Johnston, L (2004). "Modeling and Control of the Agitation-Sedation Cycle for Critical Care Patients," Medical Engineering and Physics, 26(6): 459-471, ISSN: 1350-4533.

Shaw, G M, Chase, J G, Rudge, A D, Starfinger, C, Lam, Z, Lee, D, Wake, G C, Greenfield, K and Dove, R (2003). "Rethinking sedation and agitation management in critical illness," Critical Care and Resuscitation (CCR), 5: 109-120

Chase, J G, Agogue, F, Starfinger, C, Lam, Z, Shaw, G M, Rudge, A D, and Sirisena, H (2004), "Quantifying Agitation in Sedated ICU Patients Using Digital Imaging," Computer Methods and Programs in Biomedicine, 76(2): 131-141, ISSN: 0169-2607.

Becouze P, Hann, CE, Chase, JG and Shaw, GM (2007). "Measuring Facial Grimacing for Quantifying Patient Agitation in Critical Care," Computer Methods and Programs in Biomedicine, Vol 87(2): pp. 138-147, ISSN: 0169-2607.

Starfinger, Chase, JG, C, Hann, CE, Shaw, GM, Lambert, P, Smith, BW, Sloth, E, Larsson, A, Andreassen, S and Rees, S (2008). "Model-based identification of PEEP titrations during different volemic levels," Computer Methods and Programs in Biomedicine, Vol 91(2), pp. 135-144, ISSN: 0169-2607.

Chase, JG, Starfinger, C, Hann, CE, Shaw, GM and Desaive T (2010). "Model-based prediction of the patient specific response to adrenaline," The Open Medical Informatics Journal, accepted – to appear.

Rudge, AD, Chase, JG, Shaw, GM Lee, DS, Wake, GC, Hudson, I and Johnston, L (). Impact of Control on Agitation-Sedation Dynamics, Control Engineering Practice (CEP), 2005; 13(9),1139-1149

Guyton, A C and Hall, J E, Textbook of medical physiology, 10th ed. Philadelphia; London: Saunders, 2000

LeCompte et al (2009): LeCompte, AJ, Chase, JG, Lynn, A, Hann, CE, Shaw, GM, Wong, XW and Lin, J (2009). "Blood Glucose Controller for Neonatal Intensive Care: Virtual trials development and 1st clinical trials," Journal of Diabetes Science and Technology (JoDST), Vol 3(5), pp. 1066-1081, ISSN: 1932-2968

Krinsley JS: Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. Mayo Clin Proc 2004; 79:992-1000.

Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, Van Wijngaerden E, Bobbaers H, Bouillon R: Intensive Insulin Therapy in the Medical ICU. N Engl J Med 2006; 354:449-461.

The NICE-SUGAR Study Investigators (2009). "Intensive versus Conventional Glucose ontrol in Critically Ill Patients", NEJM 360:1283-1297

Chase JG, Shaw GM, Wong, XW, Lotz TS, Lin J, Hann, CE (2006). "Model-based Glycaemic Control in Critical Care - A review of the state of the possible," Biomedical Signal Processing and Control (BSPC), Vol 1(1), pp. 3-21, ISSN: 1746-8094

Bersten, A.D., Edibam C., Hunt T. and Moran J. (2002). Incidence and mortality of acute lung injury and the acute respiratory distress syndrome in three Australian states. *Am. J. Respi.. Crit. Care Med.*, 165(4): 443-448.

Sundaresan, A. Yuta, T., Hann, C.E., Chase, J.G. and Shaw, G.M. (2009). A minimal model of lung mechanics and model-based markers for optimizing ventilator treatment in ARDS patients. *Comput. Methods. Programs. Biomed*, 95: 166-180.

Muller M, Urbanek B, Havel C, Losert H, Waech F, Gamper G (2004). Vasopressors for shock. Cochrane Database Syst Rev (3): CD003709