Health Management

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Preface

Healthcare is changing more rapidly than almost any other field. It is changing in terms of how and where the care is delivered, who is providing those services, and how it is financed. In fact, healthcare services increased for 30 percent from 1996 until 2006 and accounted for 3.1 million new jobs, which is the largest increase of any industry. Effective providing of the healthcare services requires multidimensional comprehension of a patient's situation. Skills and abilities of the medical staff, material infrastructure of a healthcare unit, social, psychological and economical context of a patient, and dynamics of diseases themselves co-create a framework for designing action strategy. Complexity of the issues is reflected by development of administrative posts related to health management.

Health management as a scientific discipline is an example of the interdisciplinary approach – it uses output of medicine, psychology, sociology, marketing and management. Its issues are considered on different levels of generality, appropriate for every science constituting this discipline:

- new ways of implementation of treatment utilizing the latest medicine achievements are developed,

- psychological reactions of a patient and his/her environment, decision-making processes by doctors, nurses, and other medical and paramedical staff are subjects of analysis aiming at finding factors facilitating and inhibiting recovery, improving patients and their families' quality of life, etc.,

- behaviors of whole social groups, their adaptation to illnesses found among its members are observed; effectiveness of strategies for solving healthcare problems implemented on a local, national or even worldwide level are analyzed.

This book contains a few chapters focusing on issues related to health management. The chapters are arranged in an order reflecting multidimensionality of issues constituting this theoretical and practical area – starting from the studies focusing on a general, administrative level, to considerations related to situations of individuals suffering from a specific illness. The discussed problems concern different age groups – children, adults and the elderly.

Among other things, the readers will find a description of tools for measurement of a healthcare project implementation rate. In chapter two issues related to care of patients suffering from chronic diseases are discussed. The third chapter partially continues the thought of the second one: the questions related to management of pain in patients with dementia are discussed - dementia is an example of a long-lasting disease, and the pain itself usually has a multifactorial background. The fourth chapter focuses on childhood pneumonia

among the children from developing countries. This document aims to provide guidelines for diagnosis and effective management of children with community acquired pneumonia so as to improve pneumonia-associated morbidity and mortality. Chapter five illustrates the advantages of focusing on early stages of a disease – the chronic kidney disease in this case. The final chapter comes from a very different thematic area – the motor industry. It describes the notion of Integrated Vehicle Health Management.

We hope you will enjoy reading this book and that it will be a useful source of information and inspiration for you and your work.

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The PRISMA France study: Is there a way to measure the implementation of integration in different countries?

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1. Introduction

In France, as in many Western countries (Vaarama & Pieper, 2006), home care services for frail older adults are fragmented and compartmentalized with services organized sectorally and vertically under different jurisdictions. In the French system, some services are associated exclusively with the social work sector and are the responsibility of the Ministry of Labour, Social Relations, the Family, Solidarity and Municipalities, Others are affiliated with the public health sector and come under the Ministry of Health and Sports. This sectoral and non-populational approach, perpetuates the compartmentalization of services, which can be seen at four levels: between the health, social and welfare sectors, between municipal and hospital workers, between the public, private-for-profit and private-non-profit sectors, and between home and institutional environments (Somme & Trouvé, 2009; Couturier et al., 2009). This makes it difficult to coordinate home care services for frail older adults, especially when home care clients receive care or services from three workers on average, and 25% of the most frail receive help from six or more (Bressé, 2004).

Various attempts have been made to improve coordination in the past twenty years. The introduction of structures such as Local Information and Coordination Centers and gerontology care networks has resulted in significant advances in the coordination of services for frail older adults (Colvez et al., 2002). However, their areas of intervention are still compartmentalized, i.e. primarily social in the first case, mainly health in the second, and both operate independently of the welfare sector, which is responsible for the Personalized Autonomy Benefit (Ennuyer, 2006).

Building on international pilot projects (Hébert 2008b; Hofmarcher et al., 2007; Johri et al., 2003; Leutz, 1999; Varrama & Pieper, 2006), the French authorities decided to test the implementation of an integrated service delivery system for older adults in so-called 'complex' situations: PRISMA-France, the French version of PRISMA (Program of Research on Integration of Services for Maintenance of Autonomy). Integrated care is defined as "a discrete set of techniques and organizational models designed to create connectivity, alignment and collaboration within and between the cure and care sectors at the funding, administrative and/or provider level" (Kodner & Kyriacou, 2000: 3). Thus integration is conceptualized as the result of a series of modelable, flexible mechanisms designed to improve continuity in managing the evolving and complex needs of frail populations (Pieper, 2006). At its core is the case manager, who is responsible for intensive management. The WHO (2000) and OECD (2007) have both made this a quality of care goal.

Today integration programs around the world vary widely. What are their objectives? What mechanisms do they employ? Who are the case managers and what do they do? For which population? How big is their caseload? How often do they intervene? With whom? With what needs assessment and service planning tools? What successes have they had? How have they failed? And why? By developing a project methodology backed by an research-action framework, the PRISMA-France pilot project provides precise answers to these different questions. A particular feature of this research-action framework is continuous feedback from a synthetic tool that defines the action plans and provides progress reports. This tool is a grid for evaluating the implementation of the components of the PRISMA integration model. It was constructed during pilot projects in Quebec, Canada, and adapted for the French pilot project. We believe that this tool, and this type of method in general, could meet a need identified in the literature, namely the need for valid tools to evaluate service integration that are transferable to different national contexts (Strandberg-Larsen & Krasnik, 2009).

This article describes the implementation and evaluation of the PRISMA integration model in France. First we describe the model as it was conceptualized, piloted and evaluated in Quebec. Second we describe the French implementation study, with a particular focus on the evaluation tool. Third we discuss the use of this methodology within an action-research framework designed to support decision-making and the move towards service integration. Finally we discuss the difficulty of deploying this action-research framework.

2. PRISMA: a model conceptualized and evaluated in Quebec, Canada

2.1 Conceptual framework: six tools and mechanisms for the integration of services for older people

According to the PRISMA model piloted in Quebec, Canada, integration is achieved when six mechanisms and tools are all brought into play (Hébert et al., 2003):

1) Coordination is the core function in constructing an integrated network for frail older adults. Because of the large number of players involved and their different professional and institutional affiliations, this coordination between partners at all levels (national, regional/departmental, local and practitioners) is a precondition of integration. The model calls for the use of regular coordination meetings in which all players involved are continuously represented depending on their level of strategic responsibilities (governance), tactical responsibilities (management) and clinical responsibilities These meetings result in decisions leading to changes in the institutional and professional practices of the players in the network.

2) Case management here is a generic 'intensive home care' function. With local support, the case managers work with a limited number of older adults (40 cases per full-time case manager). This intensive case-management is supported by the use of specific intervention tools (assessment, planning and coordination) chosen based on the objectives for living at home, as defined by the older person and his/her family with the help of professionals; Case management is a new role performed by professionals (nurses, social workers, occupational therapists, even psychologists) who are trained to be complementary, are employed by local players in the existing network, and are assigned to this function in accordance with local needs and the human and financial resources that can be brought to bear.
3) The aim of the single entry point is to improve equity and access to services. To achieve these goals, liaison and interaction between the professionals must be facilitated. Increasing the centralization of information for older people, their families and the health, social and welfare workers also improves access to services. The use of dedicated tools makes it easier to identify the population at risk of functional decline and to implement a preventive policy to monitor and manage this population.
4) Using the standardized needs assessment reduces redundant assessments and interventions and thus intrusions in clients' lives. However, getting a wide variety of professionals to use the same took requires changes in professional practices. Application of the same tools by all partners to the entire population in case management is a important integration element because these tools share clinical information and use a common language, which is necessary to guide the professionals in their work and foster mutual recognition.
5) The individualized service plan is developed after functional decline is assessed and the situation is summarized by the case manager. The case manager develops the plan with the individual concerned and in partnership with the other workers and the attending physician. The aim of this plan is to create an cross-structure coordination mechanism to organize the different client-centered interventions. Every person with a case manager must have an individualized service plan listing that person's needs and the services delivered, as well as the services required to meet unmet needs. To be a coordinated intervention planning tool, the plan must be shared with all the partners and communications between professionals must refer to this plan.
6) The primary function of the information sharing system is to provide the professionals with standardized procedures for sharing information about older people in case management, if the clients consent to the sharing of this information with the professionals working with them. The workers must define the type of information that can be shared and the sharing procedures for everyone involved. This information sharing system must be accessible to and used by all. All the players involved must have agreed on a common definition of the specifications for such a system and its implementation.

How the functions of these six integration components are operationalized is determined by a development process that is both horizontal (co-construction at national, regional and local committee levels) and vertical (two-way channel between the committees to ensure the tools and procedures are relevant and legal). In principle, with this approach it should be possible

to implement an integrated network in different service contexts, as we will now see (Somme et al., 2008b).

2.2 Results of the Quebec pilot projects

This approach was tested over nine years in Quebec in two phases, first in the Bois-Francs region, then modeled and evaluated using a quasi-experimental design combining an implementation study and a population impact study.

In the first pilot project, two cohorts of subjects in the study and comparison areas were followed for three years. The results showed a reduction in institutionalization, caregiver burden and caregivers' desire to have the care recipient institutionalized (Tourigny et al., 2004). The evaluation found small changes in how services were used: fewer trips to emergency, increased use of social services and greater use of GPs, but no significant impact on the use of hospital services or readmissions.

Based on this pilot project and after modeling the components tested, the Quebec PRISMA group organized a replication and impact study in three regions of the Eastern Townships. To measure the implementation, qualitative methods with data triangulation were used. These data were summarized and operationalized in the form of a score with a pre-determined number of points assigned to each of the six components (Hébert & Veil, 2004). Since the total was out of 100, the score represented the model's implementation rate. It was shown that the model is reproducible when the implementation rate reaches over 70% (Hébert et al., 2008a). The impact was measured by a controlled cohort study (Hébert et al., 2008b; Hébert et al., 2010). The primary end point was a combination of functional decline, death or institutionalization (Hébert et al., 2008b). The analyses showed a 7% reduction in functional decline in the experimental group with a threshold effect of about 70% of model implementation (Hébert et al., 2010). Other results did not have a threshold effect: individual autonomy increased in the experimental areas; use of emergency services and hospitalizations remained stable in the experimental areas while increasing significantly over time in the control areas; individuals in the experimental areas reported a significant increase in their satisfaction with services (Hébert et al., 2010). This integration system, which received a positive evaluation in terms of public health, was adopted across Quebec in a modified form.

3. The French experiment: implementation study and evaluation tool

Based on the evidence from the PRISMA model in Quebec, French authorities with national gerontology responsibilities decided to initiate a pilot project in France (Somme et al., 2008a; Somme et al., 2008c). This project was directed by an independent multidisciplinary team of professionals (organizational engineers, geriatrists and consultants) supported by a multi-disciplinary team of researchers (physicians, sociologists and economists). The researchers continuously monitored the project in an implementation study whose results were given to all the stakeholders, regardless of their level of involvement. The strategy used in this pilot project was based on a 'Help it happen' change management approach (Greenalgh et al., 2004). We describe this French pilot project with a particular focus on the methodology used.

3.1 Implementation study methodology

The pilot project was conducted at three sites, corresponding to the main French sociodemographic territorial configurations. They were a rural area (South of Etampes),an urban area (Mulhouse and its Nord-Est periphery) and a metropolitan area (20th district of Paris). The specific demarcation of the experimental areas corresponded to a zone covered by an existing coordination structure on which the project was based (Somme et al., 2008b).

Thus the implementation study methodology was a multiple case study, which allowed for both a comparative (by site) and overall (in relation to the French system) analysis. The aim was to be able to identify and analyze the institutional, organizational and contextual factors affecting the implementation. Each case study involved the collection and processing of so-called 'multimodal' data:

- Political/institutional watch (legislation and regulations, territorial planning and programming);
- Direct observations of coordination meetings at the national, regional/departmental and local levels;
- Semi-directed interviews with participants at the national, regional/departmental and local levels;
- Interviews with case managers and with medical, welfare and social workers working with the case managers;
- Direct observations of the single entry point and case management mechanisms;
- Analysis of de-identified case management files.

3.2 A dedicated tool: implementation evaluation grid

Based on the data collected, the implementation study monitored the implementation of the tools and mechanisms using a process evaluation method (Somme & Trouvé, 2009). This evaluation was based primarily on a synthetic indicator, namely the implementation rate of the integrated system in the territory.

This synthetic indicator is the total number from an evaluation grid that measures the density and quality of the implementation. This grid was constructed from the grid developed in the PRISMA implementation study (Hébert et al., 2008a), whose relevance had been validated by a Quebec impact study (Hébert et al., 2008b; Hébert et al., 2010). Based on a context analysis, the French configuration was modified by the multidisciplinary team in collaboration with the PRISMA team in Quebec.

The 'density' and 'quality' end points cover both the actual implementation of the six tools and mechanisms as outlined below, and also their horizontal and vertical co-construction processes in the coordination committees, taking into account the legal and administrative timeframes and thresholds attained.

More specifically, the methodological assumption was functional, i.e., the evaluation was based on the function of each component (called 'strategic variable'). These variables were then broken down into 'functional criteria', which refer to an observable and measurable purpose, behaviour or event with an attainment timeframe. Each of these phenomena is evaluated by 'indicators' measuring the presence, partial presence or absence of the function. Points are assigned to each component, variable, criterion and indicator out of a total of 100, which gives the implementation rate.

The following table shows the grid used to evaluate the implementation of the PRISMA integration model.

1. Component coordination			
Strategic variables	**Functional criteria**	**Unit basis**	**Indicators**
1.1 Presence of a coordination structure	Is there a coordination mechanism?	3 points	Unit basis breakdown: - 1 point for existence (Binary scoring system: Yes = 1 / No = 0) - 1 point for frequency (Relative scoring system: 0.25 – 0.5 – 0.75 - 1) - 1 point for organizational independence (Binary scoring system: Yes = 1 / No = 0)
1.2 Representation of the players concerned	Do the members represent all the groups of players involved in integrated service networks?	3 points	Number of groups of players represented versus the total number of groups of players concerned (Percentage scoring system)
1.3 Continuity of representation	Do the players concerned all have stable representatives?	3 points	Number of designated representatives of a group of players versus the total number of groups of players (Percentage scoring system)
1.4 Regular participation	Do the representatives participate in meetings regularly?	3 points	Stability of the representation of each group of players versus the total number of groups of players (Percentage scoring system)
1.5 Players informed of changes in services	Do the players in the strategic partnership committees and tactical partnership committees share information on the changes in services for the target groups?	4 points	Unit basis breakdown: - 2 points for respect for the agenda: acceptance versus rejection (Relative scoring system: 0.5 - 1 – 1.5 - 2) - 2 points based on judgement concerning the content of the discussion: model implementation phases and tools versus related general problems (Relative scoring system: 0.5 - 1- 1.5 - 2)
1.6 Players involved in the shared regulation of the service continuum	Do the players play a role in regulating the service continuum?	4 points	The shared regulation correspond to the levels of commitment, illustrated by the types of decisions (Scoring system: items are mutually exclusive) - 1 point for collaborative model (players involved in supply activities meeting the needs of the target populations) - 2 points for mobilization model (players involved in a 'common cause' with partners' accountability) - 4 points for social development model (players involved in the change process concerning structure and/or functioning, with commitment of the partners in action)
		20 points	

2. Component case management			
Strategic variables	**Functional criteria**	**Unit basis**	**Indicators**
2.1 Profession of case management	2.1.1 What is the gap between the number of case managers (FTE) in place compared to the objective set by the players?	4 points	Unit basis breakdown: - 2 points for commitment of organizations during implementation (Relative scoring system: 0.5 - 1 - 1.5 - 2) - 2 points for the process of matching the number of case managers / case management needs (analysis of active list/waiting list) (Relative scoring system: 0.5 - 1 - 1.5 - 2 – 2.5 - 3)
	2.1.2 Are case managers able to get quality training?	4 points	Unit basis breakdown: - 2 points for the presence of all case managers in all the training sessions (Percentage scoring system) - 2 points for the perceived quality of the training taken, evaluated by a satisfaction questionnaire (Relative scoring system: 0.5 - 1 - 1.5 - 2)
	2.1.3 Is the number of case managers (FTE) in place consistent with the steering committee's estimate?	2 points	(Relative scoring system: 0.5 - 1 - 1.5 - 2)
2.2 Functions of the case manager	2.2.1 What is the gap between the average and recommended case managers' caseload (40 cases per FTE case manager)?	5 points	(Relative scoring system with threshold: 0%: 0 points 20%: 1 point 40%: 2 points 60%: 3 points 80%: 4 points 100%: 5 points 120%: 4 points 160%: 2 points 180%: 1 point 200%: 0 points)
	2.2.2 In the case management files, are there traces of shared information and information sharing systems?	5 points	Survey of the type and frequency of shared information (Scoring system: unit basis breakdown: - 1 point for contacts with attending physician (Percentage scoring system per file) - 2 points for traceability of coordination between the practitioners (Per file and relevant workers: 0.5 - 1 - 1.5 - 2) - 2 points for all of the case management tools (Standardized Assessment Instrument, Individualized Service Plan, Shared Information System) (Percentage scoring system per file)
		20 points	

3. Component single entry point			
Strategic variables	**Functional criteria**	**Unit basis**	**Indicators**
3.1 Existence of a single entry point to case management	3.1.1 Is the single entry point the only way to access case management?	2 points	Unit basis breakdown: - 1 point for dedicated location and phone number (Binary scoring system: Yes = 1 / No = 0) - 1 point for including development of a method for disseminating conditions for access to case management (Relative scoring system: 0.25 - 0.5 – 0.75 - 1)
	3.1.2 Is the single entry point perceived as a locus of interaction and liaison between the health and social sectors?	2 points	(Relative scoring system: 0.5 - 1 - 1.5 - 2)
3.2 Single entry point as a centralizer of information about the care and services network	3.2.1 Is the single entry point a structure for access to information about the network?	3 points	Unit basis breakdown: - 2 points for information being accessible: o 1 point: to older individuals and their families (Binary scoring system: Yes = 1 / No = 0) o 1 point: to professionals (Binary scoring system: Yes = 1 / No = 0) - 1 point for method of access to information: o 0.5 point: by phone (Binary scoring system: Yes = 0.5 / No = 0) o 0.5 point: on site (Binary scoring system: Yes = 0.5 / No = 0)
	3.2.2 Is the single entry point a structure of credible information about the network?	2 points	Unit basis breakdown: a professional is responsible for defining: - 1 point: an information collection method (Binary scoring system: Yes = 1 / No = 0) - 1 point: an information updating method (Binary scoring system: Yes = 1 / No = 0)
3.3 Identification	Does the single entry point function with a dedicated, common tool to identify individuals at risk of functional decline?	6 points	Unit basis breakdown: - 2 points: defined identification procedure (Binary scoring system: Yes = 2 / No = 0) - 2 points: compliance with identification procedure for access to case management (Percentage scoring system) - 2 points: systematized procedure, including identification tool, applied to the entire older population (Relative scoring system: 0.5 - 1 - 1.5 - 2)
3.4 Triage/Referral function	Does the single entry point make it possible to coordinate access to care and services?	2 points	The professional responsible for referring requests can mobilize sufficient resources (data collection, pre-assessment, etc.). Unit basis breakdown: - 1 point: performance of the function (Relative scoring system: 0 – 0.25 - 0.5 – 0.75 - 1) - 1 point: efficacy of the referral (Relative scoring system:: 0 – 0.25 - 0.5 – 0.75 -1)

3.5 Proactive strategy	Do the entry point professionals use follow-up for prevention of functional decline?	3 points	Unit basis breakdown: - 1 point for acceptance by staff of the usefulness of this function (Binary scoring system: Yes = 1 / No = 0) - 1 point for ability to perform this function (human resources in particular available) (Binary scoring system: Yes = 1 / No = 0) - 1 point for effective follow-up preventive practices (Relative scoring system: 0.25 - 0.5 – 0.75 - 1)
		20 points	
4. Component standardized needs assessment			
Strategic variables	**Functional criteria**	**Unit basis**	**Indicators**
4.1 Common, shared assessment tool	4.1.1 Has a common tool been defined and validated by the players?	2 points	(Relative scoring system: 0.25 - 0.5 – 0.75 - 1 for definition 1.25 - 1.5 – 1.75 - 2 for definition and validation)
	4.1.2 Is there a collaborative, multidisciplinary assessment process?	3 points	(Relative scoring system: 0 - 0.5 - 1 - 1.5 - 2- 2.5 - 3)
4.2 Recognized assessment tool	4.2.1 Is the entire population targeted by case management assessed with this tool?	2 points	(Percentage scoring system)
	4.2.2 Is the assessment done by case managers recognized for access to benefits (acceptance of the RUG)?	4 points	Unit basis breakdown: - 2 points for formal recognition by the Personalized Autonomy Benefit Team (Binary scoring system: No = 0 / Yes = 1) - 2 points for form recognition by the National Retirement Fund Team (Binary scoring system: No = 0 / Yes = 1)
	4.2.3 Is the multi-dimensional assessment done by case managers recognized by all the partners?	2 points	(Relative scoring system: 0.5 - 1 - 1.5 - 2)
4.3 Older adult profile classification tool	4.3 Are the individual profiles systematically classified after the evaluation?	2 points	(Percentage scoring system)
		15 points	

5. Component individualized service plan			
Strategic variables	**Functional criteria**	**Unit basis**	**Indicators**
5.1 Individualized service plan (ISP)	Is there an ISP in the case managers' files?	3 points	Number of ISPs versus the number of case management' files (Percentage scoring system)
5.2 Explicit consent	Do the files contain a procedure for the clients' consent to the ISP objectives?	2 points	Number of clients' consents versus the number of case management files (Relative scoring system: 0.5 - 1 - 1.5 - 2)
5.3 Standardization of ISP content and updating procedures	5.3.1 Do the ISPs list the services delivered and the services needed?	3 points	Unit basis breakdown: - 1 point for the number of ISPs containing a list of services delivered (Percentage scoring system) - 1 point for the number of ISPs containing a list of needs not met by the services delivered (Percentage scoring system) - 1 point for the number of ISPs containing a summary (comparative analysis delivered/needed) (Relative scoring system: 0.25 - 0.5 – 0.75 - 1)
	5.3.2 Are there mechanisms to follow up and update the ISPs?	2 points	Unit basis breakdown: - 1 point for the definition of an ISP updating procedure (Binary scoring system: No = 0 / Yes = 1) - 1 point for the application of an ISP updating procedure (Percentage scoring system)
5.4 Formalization and effectiveness of procedures for sharing ISPs	Are the ISPs shared by all the partners?	3 points	Unit basis breakdown: - 1 point for the formalization of a procedure for case managers to share their ISPs with other practitioners (Binary scoring system: No = 0 / Yes = 1) - 1 point for the formalization of a procedure for other practitioners to access case managers' ISPs (Binary scoring system: No = 0 / Yes = 1) - 1 point for the effectiveness of the sharing and access procedures (Percentage scoring system)
5.5 Communication of the workers re: the ISP	Do case managers communicate with the other workers re: the ISP?	2 points	Unit basis breakdown: - 1 point for case managers communicating with the other practitioners based on the information and objectives in the ISP (Relative scoring system: 0.25 - 0.5 – 0.75 - 1) - 1 point for other workers asking the case managers for information and objectives in the ISP (Relative scoring system: 0.25 - 0.5 – 0.75 - 1)
		15 points	

6. Component information sharing system			
Strategic variables	**Functional criteria**	**Unit basis**	**Indicators**
6.1 Definition of standardized information sharing procedures	6.1.1 Have the players defined the type of information that can be shared with practitioners?	3 points	Definition of the information that can be shared with all those working with the individual (Relative scoring system: 0.5 – 1 - 1.5 –2 - 2.5 - 3)
	6.1.2 Have the players defined case management professional ethics procedures for the sharing of clinical informations?	3 points	Unit basis breakdown: - 1 point for the definition of a method for the individual's consent to the sharing of information about him/her (Binary scoring system: Yes = 1 / No = 0) - 1 point for the definition of measures to protect the security and confidentiality of personal information (Relative scoring system: 0.25 - 0.5 – 0.75 - 1) - 1 point for a single common procedure (Relative scoring system: 0.25 - 0.5 – 0.75 - 1)
6.2 Deployment of the tool	6.2.1 Have the players been informed of the procedures for the sharing of common information with all the practitioners?	2 points	Unit basis breakdown: - 1 point for the method of informing workers of the existence of these procedures (Relative scoring system: 0.25 - 0.5 – 0.75 - 1) - 1 point for the practitioners knowing about the existence of these procedures (Relative scoring system: 0.25 - 0.5 – 0.75 - 1)
	6.2.2 Is the information sharing system accessible to and used by all?	2 points	Unit basis breakdown: - 1 point for access to the information sharing system (Relative scoring system with threshhold: ≤ 60%: 0.25 points ≤ 80%: 0.5 points ≥ 80%: 0.75 points 100%: 1 point) - 1 point for use of the information sharing system (Relative scoring system with threshhold: ≤ 60%: 0.25 points ≤ 80%: 0.5 points ≥ 80%: 0.75 points 100%: 1 point)
		10 points	

Table 1. Grid for evaluating the implementation of the PRISMA-France organizational model

This evaluation using a 'quantified measure' is validated internally. First the data are triangulated and then scored by the research team. A first rater scores the implementation rate. A second rater scores from the source documents, blinded to the first rater's results. If there is a significant difference in the score (more than 1 point for each functional criterion), a third rater is consulted to decide in favor of one or other of the scores.

3.3 Application and results of the implementation evaluation tool

In each experimental site, the process evaluation measures the reliability, pace and stability of implementation of the integration system. To compare the processes, they are monitored over an equivalent period at each experimental site;

- T0: Pre-implementation phase from start-up (initial situation) to the training of the case managers (1 measure every 6 months);
- T1: Implementation process over 18 months including setting up the case management caseload (5 new cases/month) and testing the tools and processes (3 measures: 1 every 6 months);
- T2: Case management process functioning (2 measures 6 months apart).

In the first 18 months of the implementation study, the evaluation showed similar progress at all three sites. According to the grid, the implementation rate was between 5% and 20%. After this pre-implementation phase, the start of the case management process accelerated the implementation of the tools and mechanisms. At 36 months, the implementation rates were between 50% and 55%. This result can be viewed as the 'glass half empty' or the 'glass half full'. The perception of the level achieved depends mainly on the adoption of and familiarity with the evaluation and change support methods.

From a research perspective, to our knowledge this is the only experiment involving the transfer from one national context to another of the three components of a pilot project for integrating gerontology services: the content of the organizational system targeted by the implementation, the method of supporting the implementation, and the tool used to measure the implementation. Although it required some adaptations for use in France, it is based on the same integration conceptual framework and same components and many of the items are identical (Hébert et al., 2008a). Using a similar adaptation process, its adaptation to other contexts seems feasible and could be the basis for one of the first international methods for measuring the implementation of integration (Strandberg-Larsen & Krasnik, 2009).

4. Action-research framework with an evaluation tool to support decision-making

Developed by the research team, this grid and the rate it indicates are designed to help with action on the ground. This is why the implementation levels are included and discussed in the PRISMA-France methodology.

The integration implementation evaluation grid can be used in the territories to estimate the gap between planned and actual implementation and to identify and analyze the factors that explain local adaptations, successes and failures, which in turn can be used to modify the action plans and help in decision-making.

Because of the intrinsic characteristics of the organizational system involved, the functional evaluation grid can be useful from two perspectives. First, from the perspective of leading to

change, the aim of discussing this grid is to support and provide benchmarks for cross-sectoral and interorganizational co-construction efforts. It is a matter of creating a preparatory and proactive, i.e. participatory dynamic. Given the diversity of the socioprofessional cultures, this grid can be used to point up the negotiated compromises (Somme et al., 2008b). Also, the specific attributes of the organizational system add to the complexity because the integration calls for sharing competencies and jurisdictions. Presenting and discussing the grid helps to point up contradictions, inconsistencies or simply practical problems, even indications that certain actions are not possible.

From a public policy management perspective, in the development phase the national authorities adopted a 'Help it happen' approach, which lies between the 'Let it happen' and 'Make it happen' strategies (Greenhalgh et al., 2004). They wanted to implement an integrated system based on case management. They chose an organizational system that defines functions to be achieved and not tools and practical methods to apply. In each territory, it is the players involved in the strategic and operational coordination who define the integration tools and mechanisms with the aim of achieving the desired functions. Knowing exactly what is implemented in the territories and the factors that explain the adjustments made is thus a task they entrusted to experts outside their departments and territorial networks. The project team provides information about the modifications required to adapt the six integration components to the environment in which they are introduced, without distorting the structural principles of the integration. From the analysis of these data, the research team provides continuous, aggregate and comprehensive information regarding the quality and density of the territorial integration (Somme et al., 2008c).

The implementation evaluation grid is a tool designed to support decision-making at different organizational and institutional levels.

5. Difficulty of deploying the action-research framework

We observed that there was only partial adoption of the research-action framework in which the evaluation grid and implementation rate are tools for defining the action plans and benchmarks to support decision-making. Two main types of factors contributed to the partial adoption of this approach (Etheridge et al., 2009).

First were factors related to the organizational contexts. The overall idea of the integration model was not completely accepted. The players saw the value of taking advantage of their participation in the trial to learn from each other and develop interorganizational relationships. Two dimensions influenced their ability to consider the change process in its entirety: 1) differences in the degree of commitment to the project insofar as their own interests were represented, and 2) previous experiences with partnerships in the gerontology field. Therefore, the players had very different reasons for participating, which translated into differences in emphasis on one or more of the project components and not on the pilot project as a whole.

Second were factors related to differences in the change management approach used in the PRISMA pilot project. The 'Help it happen' approach seems to have generated two different dynamics, partly contradictory. The use of a personalized management approach tailored to the capacities of the organizational participants, designed to encourage organizations to get involved, may have fostered the adaptation of the PRISMA model to the territorial contexts

and the continuation of the project. At the same time, it may also have given the organizational participants an excuse to adopt a 'wait-and-see' posture for explicit instructions regarding the tools and mechanisms to develop. Adapting a pilot project to the particular context is crucial for the success of a change process (Greenhalgh et al., 2004), but a management approach that was too 'hands off' may have encouraged inertia and a lack of interest.

These two factors seem to explain the development of a 'strategic' attitude taken by both the organizational and institutional players towards the research-action team, who they viewed in part as directly responsible for the implementation results. This is evidenced by incomplete acceptance of the research-action framework developed in the pilot project. The detailed and comprehensive nature of the implementation evaluation method used in this pilot project may be a factor that inhibited the adoption of the overall method in which the evaluation tool was designed to be an action planning tool for the stakeholders.

These results indicate the need for and will help to define more user-friendly tools to evaluate and support the process of integrating gerontology care and services in France.

For example, in a larger pilot project launched in 2008 as part of the National Plan for Alzheimer and Associated Diseases" (2008-2012)[1] called the Homes for Autonomy and Integration of Alzheimer Patients, a more concise tool was designed to monitor the integration construction projects conducted in 17 French territories. This tool is presented below:

COORDINATION			Yes =
A strategic coordination committee meets	Yes	No	1
IF YES			
Meeting frequency is identified	Yes	No	1
IF YES			
Decisions are made at the meetings	Yes	No	1
SINGLE ENTRY POINT			
No new entry point is created during the period	Yes	No	1
An organizational analysis is done so that the local resource locations can be listed	Yes	No	1
IF YES			
A common channel for requests has been defined between the local resource locations	Yes	No	1
AND			
A standardized request processing tool has been defined	Yes	No	1
IF AT LEAST ONE YES			
A reduction in the number of entry points has been documented	Yes	No	1
AND			
The single entry point has a function for observing the population's needs	Yes	No	1
AND			
The hospital is included in the channels	Yes	No	1

[1] Downloadable at http://www.plan-alzheimer.gouv.fr/medias/m/cms/article/alzheimer/0/9/9/9/90/plan-alzheimer-2008-2012.pdf

CASE MANAGEMENT			
An organizational analysis has been done mentioning potential existing case managers	Yes	No	1
A target population for case management has been defined	Yes	No	1
IF YES to BOTH			
If there are case managers, they are supported by a strategic coordination committee already in place (question 1)*	Yes	No	1
If there are no case managers, the number of case managers needed can be estimated (needs analysis)*	Yes	No	1
IF YES			
Anticipated caseload for case managers <60	Yes	No	1
IF YES			
Physicians in private practice are involved in the process to allow for collaboration between case manager and physician	Yes	No	1
Hospital physicians are involved in the process to ensure the hospital admission/discharge interfaces	Yes	No	1
STANDARDIZED MULTIDIMENSIONAL ASSESSMENT TOOL			
An assessment tool has been defined and validated by the strategic coordination committee	Yes	No	1
IF YES			
None of the following dimensions are missing from the tool: care, functional autonomy, social environment, living conditions, mental/cognitive dimension, financial situation	Yes	No	1
IF YES			
Specific training on use of the tool has been given	Yes	No	1
INDIVIDUALIZED SERVICE PLAN			
The service plan can only exist as a function of the validation of the assessment tool	Yes	No	1
IF YES			
None of the following dimensions are missing from the tool: care, functional autonomy, social environment, living conditions, mental/cognitive dimension, financial situation	Yes	No	1
IF YES			
Unmet needs can be mentioned in the plan	Yes	No	1
INFORMATION SYSTEM			
No dedicated computerized tool has been developed without the advice of the national team	Yes	No	1
Specifications indicating the shareable information and access and network authorization have been defined	Yes	No	1
TOTAL			24

Table 2. Synthetic tool supporting change management
* These items are mutually exclusive (which explains why the maximum score is 24 and not 25).

The complex governance of gerontology policies in France means that appropriate tools are needed to measure the change towards system integration. The detailed and comprehensive

methodology employed in the PRISMA-France pilot project may be used as a paradigm for developing simpler tools, which appear to be needed for more general adoption of the structure and objectives of the integration of gerontology services.
In addition, according to some of the decision-makers involved in developing and piloting public gerontology policies, there is a "virtuous spiral" which builds on the pilot projects conducted and the knowledge generated. The PRISMA integration implementation evaluation grid was validated by an impact study in Quebec (public health outcomes included greater autonomy and satisfaction with neutral costs). The adaptation of this evaluation grid to France showed the need to construct more synthetic tools to measure the integration of gerontology services. These implementation evaluation tools may in turn undergo an impact study of the objectives and quality of care for frail older adults.

6. Conclusion

At a time when many countries are working on programs to integrate services for frail older adults, methods need to be developed to determine the exact content of these programs. Our work proposes an approach to measuring integration that can help public authorities develop, implement and evaluate a public policy for service integration.
In addition, the possibility of transferring this approach to other countries and other target populations (disabled persons, troubled adolescents, for example) could provide opportunities for comparative analyses.

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8. References

Bressé, S. (2004). Les bénéficiaires des services d'aide aux personnes à domicile en 2000. *D.R.E.E.S., Études et Résultats,* N°297 (March 2004) 1-7, ISSN 1146-9129

Colvez, A.; Gay, M.; Blanchard, N. & Fages, D. (2002). Coordination Gérontologique. Pour qui, pourquoi, comment? *Gérontologie et Société*, No. 100 (March 2002) 25-33 ISSN 0151-0193

Couturier, Y.; Trouvé, H.; Gagnon, D.; Etheridge, F.; Carrier, S. & Somme, D. (2009). Réceptivité d'un modèle québécois d'intégration des services aux personnes âgées en perte d'autonomie en France. *Revue Lien social et Politique*, No. 62 (Fall 2009) 163-174, ISBN 978-2-89035-457-9

Ennuyer, B. (2006). *Repenser le maintien à domicile; enjeux, acteurs, organisations*. Dunod, ISBN 2 10 050094 5, Paris

Etheridge, F.; Couturier, Y.; Trouvé, H.; Saint-Jean, O. & Somme, D. (2009). Is the PRISMA-France glass half-full or half-empty? The emergence and management of polarized views regarding an integrative change process. *International Journal of Integrated Care*, Vol. 9 (December 2009) e01-e011, ISSN 1568-4156

Greenhalgh, T.; Robert, G.; Macfarlane, F.; Bate, P. & Kyriakidou, O. (2004). Diffusion of innovations in service organizations: systematic review and recommendations. *Milbank Quaterly*, Vol. 82, No. 2 (December 2004) 581-629, ISSN 0887-378X

Hébert, R.; Raiche, M.; Dubois, M.F.; Gueye, N.R.; Dubuc, N. & Tousignant, M. (2010). Impact of PRISMA, a coordination-type integrated service delivery system for frail older people in Quebec (Canada): A quasi-experimental study. The Journals of Gerontology. *Series B, Psychological Sciences and Social Sciences,* Vol. 65B, No. 1 (January 2010) 107-118, Print ISSN 1079-5014

Hébert, R.; Veil, A.; Raiche, M.; Dubois, M.F.; Dubuc, N. & Tousignant, M. (2008a). Evaluation of the implementation of PRISMA, a coordination-type integrated service delivery system for frail older people in Quebec. *Journal of Integrated Care*; Vol. 16, No. 6 (December 2008) 4-14. ISSN: 1476-9018

Hébert, R.; Dubois, M.F.; Raiche, M. & Dubuc, N. (2008b). The effectiveness of the PRISMA integrated service delivery network: preliminary report on methods and baseline data. *International Journal of Integrated Care*, Vol. 8 (February 2008) e01-e015, ISSN 568-4156

Hébert, R. & Veil, A. (2004). Monitoring the degree of implementation of an integrated delivery system. *International Journal of Integrated Care,* Vol. 4 (September 2004) e01-e07, ISSN 568-4156

Hébert, R.; Durand, P.J.; Dubuc, N. & Tourigny, A. (2003). PRISMA: a new model of integrated service delivery for the frail older people in Canada. *International Journal of Integrated Care*, Vol. 3 (March 2003) e01-e08, ISSN 568-4156

Johri, M.; Beland, F. & Bergman, H (2003). International experiments in integrated care for the elderly: a synthesis of the evidence. *International Journal of Geriatric Psychiatry* Vol. 18, No. 3 (March 2003) 222-235, ISSN 0885-6230

Kodner, D-L. & Kyriacou, C.K. (2000). Fully integrated care for frail elderly: Two American models. *International Journal of Integrated Care*, Vol. 1 (November 2000) e01-e019, ISSN 568-4156

Leutz WN (1999). Five laws for integrating medical and social services: lessons from the United States and the United Kingdom. *Milbank Quarterly* , Vol. 7, No. 1 (March 1999) 77-110, ISSN 0887-378X

OECD Hofmarcher M, Oxley H & Rusticelli E. Improved health system performance through better care coordination. Paris: OECD; 2007 [online]: http://www.oecd.org/dataoecd/22/9/39791610.pdf

Pieper, R. (2006); Integrated care: concepts and theoretical approaches. In *Managing Integrated Care for Older Persons. European Perspectives and Good Practices*, Vaarama, M. & Pieper, R. (Eds.), 26-53, STAKES, ISBN 951-33-1584-3, Helsinki

Somme, D. & Trouvé, H. (2009). Implanter et évaluer une politique d'intégration des services aux personnes âgées : l'expérimentation PRISMA France. In *L'évaluation des politiques publiques en Europe. Cultures et Futurs*, Fouquet, A. & Méasson, L. (Eds.), 385-395, L'Harmattan, ISBN 978-2-296-09069-9, Paris

Somme, D.; Trouvé, H.; Couturier, C.; Carrier, S.; Gagnon, D.; Lavallart, B.; Crétin, C.; Hébert, R. & Saint-Jean, O. (2008a). PRISMA France: Programme d'implantation d'une innovation du système de soins et de services aux personnes en perte d'autonomie. Adaptation d'un modèle d'intégration basé sur la gestion de cas. *La Revue d'Épidémiologie et de Santé Publique,* Vol. 56, No. 1 (February 2008) 54-62, ISSN 0398-7620

Somme, D.; Trouvé, H.; Périsset, C.; Leneveut, L.; Lavallart, B.; Kieffer, A.; Lemonnier, S. & Saint-Jean, O. (2008b), Implanter c'est aussi innover : PRISMA France et la recherche-action. Les Réseaux, *Revue Gérontologie et Société*, No. 124 (September 2008) 95-107, ISSN 0151-0193

Somme, D.; Trouvé, H.; Couturier, C.; Carrier, S.; Gagnon, D.; Lavallart, B.; Crétin, C. & Saint-Jean. O. (2008c). PRISMA France: Adapting the PRISMA integration model to the French health and social services system. In: *Integration of Services for Disabled People: Research Leading to Action,* Hébert, R.; Tourigny, A. & Raîche, M. (Eds.) 511-526, EDISEM, ISBN 978-2-89130-215-9, Québec

Strandberg-Larsen, M. & Krasnik, A. (2009). Measurement of integrated healthcare delivery: a systematic review of methods and future research directions. In: *International Journal of Integrated Care*, Vol. 9 (February 2009) e01-e10, ISSN 1568-4156

Tourigny A., Durand P-J., Bonin L., Hébert R. & Rochette L. (2004). Quasi-experimental study of the effectiveness of an integrated service delivery network for the frail elderly. *Canadian Journal of Aging*, Vol. 23, No. 3 (Fall 2004) 231-46. ISSN 0714-9808

Vaarama, M. & Pieper R. (Eds.) (2006). *Managing integrated care for older people*. STAKES, ISBN 951-33-1584-3, Helsinki

WHO The World Health Report 2000 – Health systems: improving performance. Geneva: World Health Organization; 2000. [en ligne]: http://www.who.int/whr/2000/en/index.html

A proposed care model for a complex chronic condition: multiple chemical sensitivity

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1. Introduction

One of the major challenges to delivering effective health care to patients with complex, chronic health problems is that health systems have been designed to deal with acute episodic illness. This has lead to increasing specialization in treatment of disease, focused on individual body systems and indeed one part of one organ. When a person becomes acutely ill and requires expertise that cannot be managed by a primary care physician they are referred for specialized care. As the population ages we are seeing more chronic health conditions which require long term management, often punctuated by episodes requiring acute care. As the burden of chronic disease has increased it has been recognized that management becomes more complex when there are interacting problems like hypertension, cardiac disease and diabetes. Individual "diseases" are more easily managed, but when there are multiple diagnoses, management becomes more difficult. Fortunately many of these chronic conditions have clear guidelines for monitoring and treatment, and even where there can be several problems in the same patient the guidelines are followed. However, patients who develop more difficult problems in more than one body system often end up with treatment from multiple specialists. Coordination of the efforts of the various specialists usually rests in the hands of primary care physicians, which presents many challenges (Henningsen et al 2003, Verhaak et al. 2006). In Canada, family physicians provide primary care and for the most part work independently, not within a team of other health professionals. Most family physicians have a heavy workload and usually see many patients during fairly short visits. Patients with multiple, interacting problems present a major challenge for family physicians(Fink & Rosendal 2008). When someone is chronically ill with multiple conditions, they often see different clinicians at different sites. This increases the risks of errors and of poor care coordination. Undoubtedly this increases suffering for the individual and higher health care costs for society. These issues have been recognized in the elderly population and the speciality of geriatrics has developed which specializes in the management of the frail elderly (Rockwood et al 1994). Frailty is more likely with more health problems or deficits (Rockwood et al 2004), and the most frail individuals present greater challenges in management.

No such specialization has developed in dealing with younger patients with multiple interacting problems and it is much more difficult for primary care physicians to manage poorly understood chronic illnesses. Often these chronic illnesses are not recognized as specific illnesses or diseases, but only as chronic problems with medically unexplained symptoms. These kinds of problems present major challenges and we know that they are common in Western populations. Chronic fatigue syndrome is known to affect between 400,000 and 900,000 adults in the United States (Jason et al 1999, Reyes et al 2003). About 16% of Californians report that they are unusually sensitive to chemicals and 6.3% have been diagnosed with environmental illness (Kreutzer et al 1999). Hypersensitivy to chemicals leading to illness has also been reported to affect about 13% of a population in Georgia, United States (Caress and Steinemann 2004). Chronic illnesses, which are not well understood are common problems which place a significant burden on health care systems. There are several, major challenges to effective care. It takes longer to make a diagnosis (Stockl 2007), to identify solutions and offer recommendations for the multiple problems. Another issue is being able to offer treatment recommendations which are evidence based and in accordance with published guidelines. This is impossible if the patient seeking help has medically unexplained symptoms, or is diagnosed with a condition such as multiple chemical sensitivity, chronic fatigue syndrome or fibromyalgia, since widely accepted guidelines do not exist. So what kind of care can be provided when the physician is faced with a patient who is experiencing life-changing ill health and who reports extensive suffering and disability? The physician may well ponder various questions such as "Which specialist is able to help?" or "What can I offer for treatment?" or "Where can I find the time to listen to the various complaints?"

In one prospective study of 300 new patients referred to a neurology clinic, 11% had symptoms which were not at all explained by organic disease and a further 19% were only somewhat explained (Carson et al 2000). The authors concluded that these patients were disabled, distressed and deserved more attention. Being unable to fully understand the disease process or to make a specific diagnoses should not prevent provision of appropriate health care. Indeed there are reports of various approaches to help individuals and alleviate suffering, for example by offering cognitive behavioral therapy (Martin et al 2007). Sumathipala (2007) reviewed published literature for the highest level of evidence on the efficacy of treatment for patients with medically unexplained symptoms, and concluded that there was more evidence for cognitive behavioural therapy improving the health of these patients than for any other form of therapy.

The term medically unexplained symptoms was probably first used by de Figueiredo (1980) when describing a case of Briquet's syndrome, a recognized psychiatric disease. Since that introduction, the term has been used to describe any condition that lacks structural pathology in the tissues (Nettleton 2006; Binder 2004; Smythe 2005). It is obvious from the literature on medically unexplained symptoms, that many authors have a psychological or psychiatric background, and therefore interpret the illness as being secondary to psychopathology. There is little discussion of the biological aspects of the illnesses diagnosed in patients with unexplained medical symptoms. Another label that is applied to these difficult and complex patients is somatization disorder, or that the symptoms are manifestations of somatization. To identify the illness as somatization disorder is not appropriate for this patient population with chronic ill health. To make such a diagnosis symptom onset must occur before the age of 30. Furthermore common associated features

include loss of touch and pain sensation, inconsistency in history and antisocial behaviour (DSM-IV-TR 2000). Patients with chronic health problems which include the diagnoses of multiple chemical sensitivity, fibromyalgia and chronic fatigue syndrome do not show these features and there is no evidence that psychiatric or psychological therapies alone cure the problems. Somatization disorder is not an appropriate diagnosis but might be used as a descriptive term to define the illness behaviour in which an individual communicates psychological distress through unexplained physical symptoms (Ford 1997; Bluui and Horopf 1997). It is recognized that in a wide variety of health problems patients can experience some relief of suffering with appropriate psychological treatment.

A survey of chronically ill adults in eight different countries reviewed the experiences of patients with chronic conditions and with complex health care needs (Schoen et al 2008). These authors pointed out that the goals for treatment of chronic illness are different from managing acute episodic illness. When health systems are designed to deal with acute illness the goal is usually cure rather than seeking to prevent complications and delaying deterioration. The major intention of any form of health care is to alleviate suffering which is frequently achieved in a system focusing on acute care when cure is possible. When cure is not possible,this becomes more difficult and suffering may increase secondary to inappropriate treatment or iatrogenic complications. This is well recognized in the management of the frail elderly in acute hospitals. It is not surprising that the study of Schoen and others (2008) found significant variation in care of patients with chronic illness in different countries. The authors conclude that there is a need to integrate care for the chronically ill patient around the patient, supported by information systems that provide timely and relevant information and enable effective and efficient care. Integrating care around a patient means adopting a biopsychosocial approach to care, paying equal attention to biology and psychology. Patients are referred to the Nova Scotia Environmental Health Centre because they are ill and suffering. In the absence of any recognized effective approach to care we adopted the concept of person-centred patient care. In this chapter we review the development of this approach in the management of patients with multiple chemical sensitivity and offer it as a model for management of chronic disease.

2. Multiple Chemical Sensitivity

The Nova Scotia Environmental Health Centre was established in 1994 to provide care for environmentally sensitive patients and to conduct research into the diagnosis, pathogenesis and management of patients with multiple chemical sensitivity. The Department of Health of the province of Nova Scotia was responding to the need expressed by patients and physicians. Since the opening of the center the demand for clinical care has been high.

Multiple chemical sensitivity has been identified as a disorder which is characterized by reactivity to environmental chemicals. Controversy exists as to the etiology and possible pathogenesis. Controversy continues as to whether it is a disease or an illness, and in the absence of identifiable structural pathology, most refer to it as an illness. If it is accepted as a distinct problem then what is the pathogenesis? Is it physical or psychological? This example of Cartesian dualism has been discussed for many years by physicians, patients and society at large. Since this is a poorly understood problem, many have concluded that this disorder is psychological and should be treated as a psychological problem. Yet there is little evidence that psychological or psychiatric treatment alone has helped patients

(Davidoff & Fogarty 1994). Labelling a difficult to understand problem as a psychological problem is often problematical and once the Nova Scotia Environmental Health Centre was established in 1994 many patients were referred on their insistence that they were not psychologically ill, that there was "something else going on". It soon became clear that some patients were extremely stressed or anxious, and some were depressed. However, because of their traumatic experiences with other health professionals, it was difficult at first to address these issues without first establishing an alliance with the patient. Any approach was seen as yet another physician diagnosing the illness as being "all in your head."

In order to be able to address psychological issues, if present, it became necessary to gain trust and confidence and to validate the patient's illness experience. It was not difficult to recognize that the patients referred to the Nova Scotia Environmental Health Centre and who fulfilled the criteria for a diagnosis of Multiple Chemical Sensitivity, were ill. Indeed, it is generally accepted that people diagnosed with this condition are ill and experience a wide range of symptoms, even if there is no agreement as to whether this is a single disease. Mark Cullen(1987) provided a research definition of this condition, which he referred to as multiple chemical sensitivities. This has led to other, improved definitions, which are more valuable in clinical settings to establish a diagnosis (Nethercott et al 1993, Bartha et al 1999).

The best available case definition was reached by consensus and published in 1999 (Bartha et al 1999). Multiple chemical sensitivity is diagnosed in a patient when the following six criteria are met;

1. The symptoms are reproducible with repeated chemical exposure
2. The condition is chronic
3. Low levels of exposure result in manifestations of the syndrome
4. The symptoms improve or resolve when the incitants are removed
5. Responses occurred to multiple, chemically unrelated substances
6. Symptoms involve multiple organ systems

The diagnosis of Multiple Chemical Sensitivity is made when all six criteria are fulfilled and can be made alongside other diagnoses such as asthma, allergy, migraine, chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome, depression, panic attacks or interstitial cystitis. Implicit in this consensus definition is the recognition that there is wide variability in the clinical presentation and in the degree of disability among patients. Disability can be minimal or total. The experience at the Nova Scotia Environmental Health Centre is that up to half our patients are disabled to the extent that they have to stop work or discontinue education. Symptom severity can vary from being mild to severe, including life-threatening anaphylaxis. Patients with multiple chemical sensitivity experience physiological dysfunction in various body systems manifest by the development of symptoms upon exposure to a triggering substance or a new environmental situation. Exposure can be by ingestion, inhalation or topical application to the skin. Environmentally sensitive individuals can experience dysfunction in more than one body system at the same time. Irritation of the airways can lead to rhinitis, sinusitis, cough, hoarseness, laryngeal stridor or asthma. Central nervous system dysfunction, present in most patients, leads to complaints of being unable to concentrate, to think clearly, to complete multistep tasks, to recall items from memory or to lay down new memories. This collection of symptoms is often referred to as "brain fog". Inevitably there are mood changes in association with the symptoms, such as irritability, anxiety and depression.

In a detailed study of 351 patients referred to the Nova Scotia Environmental Health center and diagnosed with multiple chemical sensitivity, it was found that 80% of the patients were female and 37% fell within the 40 to 49 year age group (Joffres et al 2001). The major symptoms experienced by this patient population were divided into two categories –

1. Generalized symptoms such as fatigue, difficulty in concentrating, forgetfulness and irritability:
2. Irritative symptoms such as sneezing, hoarseness of voice and irritated eyes.

In the medical literature, occupational exposure has been reported to lead to the development of multiple chemical sensitivity, for example 13% of 160 solvent exposed workers (Gyntelberg et al 1986). Multiple chemical sensitivity has also developed in workers exposed to organophosphate pesticides(Cone and Sult 1992; Tabershaw and Cooper 1966) and tunnel workers exposed to gasoline contaminated soil (Davidoff et al 1998). However, in at least half the patients seen at NSEHC there is no identifiable toxic exposure. Although etiology is often unclear and pathogenesis is obscure, MCS patients who are ill share common features. The most obvious is the reactivity to modern environments that the majority of the healthy population can tolerate.

As noted above patients who are diagnosed with multiple chemical sensitivity also have overlapping problems such as fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, interstitial cystitis, asthma, reactive upper airways dysfunction, irritant vocal cord dysfunction, temporomandibular disorders, myofascial pain syndrome, migraine, chronic pain disorder, or post-traumatic stress syndrome. These patients have often been categorized as having medically unexplained symptoms or somatization. Yet it is possible to demonstrate biological changes of physiological dysfunction. For example in the patients with multiple chemical sensitivity, hypersensitivity to chemicals can be objectively demonstrated. This is done by exposing individuals to the presence of common household products without their knowledge (but with their consent and full ethical approval) and monitoring physiological changes (Joffres et al 2005). This is important in many patients to be able to obtain objective confirmation of hypersensitivity, but also because the state of high arousal in the nervous system can also be identified. This helps in management. There is evidence in the medical literature that other biological changes are found, such as increased nociceptive flexion reflex in fibromyalgia (Desmeules et al 2003, Banic et al 2004), in chronic pain and whiplash (Banic et al 2004), and in irritable bowel syndrome (Coffin et al 2004). There may be an absence of structural pathology, yet dysfunction can be objectively demonstrated. The common pathophysiological finding in these groups of patients is central sensitivity, and the illness is best described as Central Sensitivity Syndrome (Yunus 2000, 2007, 2008). It is obvious that these patients who are chronically ill and disabled have a mix of biological changes and psychological issues. It will become clear that if this is the case then to alleviate suffering, physical and psychological issues need to be addressed together.

3. Many challenges to health care

It can be seen that the care of patients with multiple chemical sensitivity offers many challenges. Even though there is a great deal of controversy with regards to the very existence of this health problem, patients are identified with complex chronic ill health and share similar clinical features and symptoms. These patients attend the Nova Scotia Environmental Health Centre seeking help in understanding their health problem and for

alleviation of suffering. A continuing challenge has been the belief that the Nova Scotia Environmental Health Centre will offer treatments that are not available elsewhere and will be succesful in eradicating the problem. Many patients exhaustively search for a cure or for the reason that they are ill and their focus often is narrowed down to specific symptoms. It is a great challenge for any patient to accept the limited effectiveness of treatment for the various symptoms. Furthermore, that the best route to better health lies in addressing aspects of their health which do not seem to be immediately linked to any specific symptoms or single diagnosis. Closely linked to this is the challenge to accept responsibility for self-managment and decreasing reliance on health professionals.

As our experience with patients referred for consultation continued, and the diversity of patients increased, more challenges to care became apparent. Most patients had seen a wide variety of health professionals yet remained symptomatic and ill. A high percentage of patients stated that not only were they intolerant of most modern buildings, including hospitals and doctors offices, but they found that any treatment offered often made them worse. It is extremely challenging for a physician to be faced with an ill, disabled patient who cannot access usual health care facilities or refuses to take a pharmaceutical that would normally be considered appropriate for relief of symptoms. When symptoms are found in multiple body systems, the level of distress in the patient increases and the challenges to the physician rise exponentially. This leads to more visits to a doctor's office, to hospital or to the emergency room. At the time of referral to the Nova Scotia Environmental Health Centre the mean physician visits per patient were 2 to 3 times the average for the population of Nova Scotia (Fox et al 2007). Many patients had seen a number of different health professionals but were still seeking help, and reported increasing difficulty in finding health facilities that they could tolerate. Prior to the establishment of the Nova Scotia Environmental Health Centre it was determined that the only way to begin to understand the nature of this illness and to be able to help individuals was to create a facility which provided an environment in which environmental stress was reduced to a practical minimum. This has been another challenge, the need for continued vigilance in maintaining acceptable air quality and the financial constraints related to this.

As more patients were seen, it became clear that the current approaches to treatment were unsatisfactory, and no guidelines were available which would identify which treatment was useful. Some treatments had been developed which were claimed to reduce environmental sensitivity but for which there was little supportive evidence. Sometimes treatment was counter-productive, not only failing to help patients get to a higher level of health, but aggravating symptoms. For example, treating patient as if allergic may do more harm than good. Patients who are extremely sensitive to modern environments that the majority of the population tolerates, usually state that they are allergic. However there is no evidence that allergic mechanisms account for the symptoms of chemically sensitive patients. This belief has led to the development of diagnostic and treatment methods closely related to the concept of allergy. This presented major challenges since treatment methods were controversial and research into the various approaches was essential before treatment could start. An example of this was the use of a form of testing for sensitivities known as provocation/neutralization. Some treatment options depended upon the accuracy of this testing and it was an expensive proposition for any patient. Early research revealed the difficulties with this approach and we were unable to validate the claim that chemical sensitivity could be accurately defined by this form of testing (Fox et al 1999). Testing

provided results which were unreliable and we had to discard one of the mainstays of treatment and seek other approaches.

Another challenge to appropriate treatment occurs when the illness is looked at as a purely physical phenomenon, for example as a result of toxic overload and psychological aspects ignored. Conversely, if it is concluded that the symptoms are not physical, but psychological, then the label of "somatization" is applied. This does not improve diagnostic accuracy nor help in understanding the patho-physiology. In this case focusing on the psychological or emotional aspects alone does nothing to relieve symptoms. An individual who recognizes that a scent triggers asthma or migraine is advised to avoid exposure, rather than to enter counseling and continue being exposed.

Despite the many challenges, we recognized that all patients showed a varied mixture of problems which included evidence of structural pathology, no structural pathology but clear evidence of physiological dysfunction or evidence of psycho-pathology and associated psychosocial issues. A major challenge in health care of these patients was to decide which type of physician should be providing care. Family medicine is only speciality in medicine which trains physicians to be prepared to manage patients of all ages, either sex and any kind of problem. The various constraints for primary care physicians in dealing with these complex problems have already been discussed. There are no other specialists available with appropriate training in the types of chronic illness that were being referred to the environmental health centre. As patient needs were identified, the team of health professionals expanded. However the approach retained features of the traditional medical model in as much as the consulting physician remained the source of entry into the various treatment programs at the centre. We need appropriately developed guidelines or protocols for care, but treatment to alleviate suffering cannot wait until all the evidence is firmly in place. This is a continuing challenge and care which does not harm has been developed, accompanied by research to evaluate the different approaches. Hopefully clear management guidelines may be developed in the future.

4. The emergence of multidisciplinary management for multiple chemical sensitivity

Programs of care, with emphasis on patient education and self-management, were developed, evaluated and modified as required. Initially, the rationale for education of patients to reduce environmental stress, was the evidence accumulated from many patients that there were triggers in the environment that led to symptoms and worsening of health. Furthermore, reducing environmental stress reduced symptoms and helped patients restore health. Physicians and nurses therefore educated patients on how to manage, and create a personal environment which was free of identifiable triggers like fragrances, thus reducing the environmental stress to a practical minimum. Patients were not educated to shut themselves away even though many had done so for some time before being seen. All patients receive some basic educational material on management of their health problems. Since the approach to care begins with a shift towards healthy lifestyle choices and, as the clinic is dedicated to care of individuals with environmental senstivities, patients were required to change personal care products to fragrance free products If symptomatic relief was possible, then it was offered, obviously dictated by the nature of the problem and the tolerance of the individual to the different approaches. Examples of symptomatic relief

included the provision of medication for pain relief. However, many patients had limited tolerance to pharmaceuticals and in this situation, analgesia was provided using topical preparations of pharmaceuticals. If a magnesium load test revealed high retention of administered magnesium, then parenteral magnesium was given to relieve fatigue and generalized muscle pains. Obviously other conditions might be identified at the time of initial consultation, such as celiac disease or hypothyroidism and these were treated appropriately. Some patients were obviously de-conditioned as a result of their illness and it was logical to advise exercise. During physiotherapy assessments it became clear that reactions identical to those triggered by the environment, could be triggered by exercise. We also recognized that reactions and symptoms could be triggered by emotions, even in a clean environment. Many patients complained of "brain fog" and so psychology was added. The increased patient case load and limited number of accessible personnel lead to development of programs in which groups could be taught skills of self management and ways to increase their resiliency and self-efficacy. Patients are taught practices that can be continued at home, or when less sensitive, in the community.Our overall approach in groups and for individuals was based on changing behaviour and increasing capacity to cope.

A significant number of our patients were disabled and could not prove their illness with objective testing and evidence of structural pathology. A rehabilitation specialist who was able to coordinate the various aspects of rehabilitation was one of the first additional professionals to be added. Over time other professionals have been added to the health care team, namely dietary and occupational therapy. As mentioned, in the early days the physician referred the patients to the different programs as problems were identified. Some patients were found to be profoundly dysfunctional with limited tolerance for any activity. They required individualized therapy to help control symptoms and assist in the process of change or transformation. For example certain forms of psychotherapy, craniosacral therapy, therapeutic touch or guided imagery may shift perceptions from illness and despair to one of hope for improved health.

Patients were offered programs to learn skills to manage stress, and to retrain the often dysfunctional autonomic nervous system. One such workshop teaches the HeartMath® tools such as FreezeFrame® and Heart Lock in® (Childre and Martin 1999). The techniques or tools learned in these programs are known to improve focus, creativity, and emotional clarity, as well as reducing stress and anxiety. They are easily learned techniques and after the initial workshop patients can practice and check their abilities when attending the centre for another appointment, by using a computer program - emWave PC. As patients monitor their own progress they are also learning important principles of self-management. An important aspect of the workshop is to present the scientific evidence that it is possible to reduce anxiety and to alter hormone levels (increasing DHEA and reducing cortisol) by regular practice of these techniques and without the necessity of additional pharmacotherapy (McCraty et al 1998). The HeartMath tools help in the process of change, and integration of mind and body. From the initial consultation, throughout all treatment programmes, we emphasize the importance of both mind and body, not separate but integrated.

This approach is the basis of another program that has been developed, based upon the mindfulness based stress reduction work of Jon Kabat Zinn (Kabat-Zinn 1990. Kabat-Zinn et al 1992). This program runs for 10 weeks and is called the Body mind awareness program (BMAP) and teaches mindfulness meditation and yoga. Evaluation has shown the benefit of

this approach with reduction of symptoms and improved coping skills (Sampalli et al 2009). Since our patient population is drawn from all the Atlantic Provinces with some patients coming from other parts of Canada, this program cannot be completed by these patients, since it requires attendance one day a week for 10 weeks. We also offer a 4 day intensive program to introduce patients to these techniques and practices and to encourage continued self-learning and practice.

Although we may not fully understand all the contributing factors to illness in any individual, we can identify factors that limit health and decrease resiliency. For example, inability to express emotions or suppression of emotions may lead to physical symptoms (Abbas et al 2009) which can be helped with short term dynamic psychotherapy. If this is identified as an issue during the psychosocial assessment then appropriate psychotherapy is recommended. With improved health, reduction of symptoms and decreased disability return to work can be considered. If the person became ill in the workplace where there was significant environmental stress, such as an autobody shop or hairdressing salon, then it is likely that a change in employment is necessary to maintain health and prevent recurrence of illness. In this situation a group workshop, Prior Learning Assessment Recognition, which helps individuals take full stock of their accomplishments and potential, is offered to assist in change and prepare for work return.

It is difficult to provide a simple prescription to move a patient from the desire for recovery to the pre-morbid state of health, to a willingness to explore, discover and accept a new state of wellness. After some initial therapy it is hoped that the patient develops the capacity to participate in group programs which help in continuing transformation as they learn to live more fully with their present condition and focus on potential rather than limitations. We have found that as perceptions shift, and allostatic load decreases, health improves.

5. Impact of treating the whole person

Out of necessity, the treatment approach at the Nova Scotia Environmental Health Centre incorporated the concept that in managing health, we cannot separate mind from body. Furthermore, our medical interests could not be restricted to those illnesses that only show clear cut and easily demonstrable structural pathology. There has always been a need to carefully evaluate the programs that were introduced and we have evaluated the impact of this multidisciplinary treatment approach using a symptoms questionnaires (Fox et al 2007). This work has shown that after the patients begin treatment at the centre, the number of physician visits, of all types, reduced. We looked at 563 patients who had been referred to the centre by physicians in the province of Nova Scotia. Each patient completed a 217 items symptom questionnaire of 13 body systems (Joffres et al 2001). Each patient at the NSEHC had a health care insurance number. This number was sent to the agency in charge of encryptions along with a unique identification number. The encrypted number was then sent to the population health research unit, Dalhousie University, which linked the administrative data through the encryption number and merged with basic questionnaire variables using the identification number. The population health research unit was responsible for analysis. There was no possibility to link individual data with the healthcare utilization information at any stage of the process, thus protecting privacy of each patient. Ethical approval to perform these record linkages was obtained from Dalhousie University Research Ethics Board. Individual patients were included in the study if they were eligible

for health care coverage in the entire pre-and post-periods of study. This insured that patients were eligible to receive the same services in both periods. The pre-period was data that were extracted from one year before consultation, and the post-period was indicative of the information until 2002. Three cohorts of patients were studied namely 1998 1999 and 2000 and followed until 2002. The mean physician visits in the 1998 and 1999 cohorts dropped close to the Nova Scotia average in the year 2000 and stayed for the next two years.
By the time the study took place, the Nova Scotia Environmental Health Centre had been in existence for several years and the multidisciplinary, holistic approach to management had gradually developed in response to our clinical experience. Review of the number of physician visits before and after admission to the centre indicated that these patients with "untreatable illnesses" were responding to some form of treatment. At least, the number of physician visits was dropping. We also looked at the cost of healthcare. All physician/patient encounters were extracted, not just office visits. Multiple records with the same medical services insurance, date of service, location, and doctor were considered as a single visit, with the cost of the multiple records summed accordingly. Data for the Nova Scotia population were extracted in a similar fashion. The denominator used to calculate rates for the Nova Scotia population referred to the mid-year population of those eligible for health coverage in the province. Prevalence rates for hospital diagnoses were based on the primary diagnostic field only. Age for the Nova Scotia sample was calculated at the mid-fiscal year and for the patient cohorts was calculated as age at first visit. For the 1998 cohort, standardized costs in the Nova Scotia Environmental Health Centre population dropped from $527to $328 per person (38%) between 1997 and 2002, whereas provincial averages increased by 19% during that same period. The 1999 cohort showed a decrease of 8% from $403 to $371, whereas the provincial average increased by 14%. The 2000 cohort shows the environmental stress(patient) group decreasing by 21% from $528 in 1999 to $418 in 2002. Overall, in a two-year period preceding and following active involvement in the NSEHC, standardized costs for physician care fell by 17%, whereas they increased by 9% in the Nova Scotia population. We found that there was a decrease in costs for both specialists and general practitioner visits, but the decrease for specialist costs was not as sharp.
The decrease in mean physician visits was seen at all levels of symptom severity scores, and was more important in those with high initial scores. The symptom severity scores were obtained from the questionnaire. Symptom scores were calculated as the frequency of occurrence of symptoms since the beginning of the illness (scale 1-4; rarely, from time to time, most of the time, all the time) multiplied by the severity (Scale 1-3 low, moderate, high). Therefore the maximum score for each question was 12, and the minimum zero. A global score was calculated for each patient, which was the mean score computed as the sum of all scores divided by the number of questions.
This study has limitations in that it was not possible to complete a full cost benefit analysis. Although we cannot conclude that there was a decrease in total healthcare costs our data certainly suggests a reduction in physician visits.
At the time of developing the questionnaire for our patient population we completed a validation study to determine effectiveness and sensitivity of the questionnaire. In addition to the 217 symptom questions in 13 sections there were opportunities to complete open ended questions. Patients were asked to complete this questionnaire at the time of their illness and they often took 2 to 3 hours for completion. Such a lengthy questionnaire was not practical for repeated use in follow up, and so we identified the top 15 symptoms and used

them for follow up. There are 30 questions in total in this abbreviated questionnaire, NSEHC-BREF, with 22 questions on symptoms and 8 questions on the overall health. The maximum score for each question is 12, frequency multiplied by severity. The lowest score possible is 0. A decrease in the score indicates improvement. SAS 9.1 was used to conduct this analysis of the results.

The average time for completion of the abbreviated questionnaire is 15 minutes. Our intention was to use this questionnaire in an attempt to capture changes over time, which would be equated with better health. We approached approximately 500 patients with a diagnosis of multiple chemical sensitivity (Fox et al 2008). It should be noted that many of these patients had other chronic conditions such as chronic fatigue syndrome or fibromyalgia. All patients had completed the original questionnaire, and were grouped into the following categories

1. 6 month to 1 year of treatment at the Centre
2. 1 to 2 years
3. 2+ years treatment.
4. Discharged

A total of 183 patients the first three categories, still receiving treatment at the Nova Scotia Environmental Health Centre were included in the study and 109 patients who had been discharged. Patients showed a statistically significant improvement in the overall health in such categories as health since ill, too ill to do housework and limited contact with people to avoid exposures. Some symptoms improved early on, showing statistically significant change within the first year such as the complaint of a stronger sense of smell or a tight chest. Some improvement of irritative symptoms such as nasal stuffiness and sinus congestion were observed in the one year and above group. Loss of voice, hoarseness and irritated eyes, took longer to improve showing sudden improvement in the 2+ and discharged groups.

Symptoms which might be considered more generalized, such as difficulty in concentrating, difficulty in making decisions, tiredness not relieved by sleep, muscle spasms and cramps showed significant improvement in all categories of patients. Irritability, forgetfulness and trouble finding the right words took slightly longer but did show significant change after one or two years of treatment. When fatigue is identified as a problem or tiredness without energy, improvement was shown in the group who were discharged or who had been in treatment for more than two years. They were inconsistent changes in some of the other symptoms.

It is challenging to measure change in chronic health conditions such as multiple chemical sensitivity, particularly when there are multiple diagnoses and multiple care providers. We know that with the passage of time, individuals change. This study helps us to identify whether health changes occur with time and the nature and extent of symptom changes. In the future it will be important to look at control populations to determine the effect of passage of time alone on overall health. Furthermore, we need to look more closely at the different aspects of our management approach to determine what is most important.

6. Introduction of multidisciplinary assessment at the start of treatment

With the passage of time it became clear that some issues were not addressed until after the patient had been attending the centre for some time, leaving open the possibility that if dealt

with earlier, improvement would have started earlier. Furthermore, if the initial focus of treatment was only on physical issues at first, we wondered if this contributed to the reluctance of some patients to consider the impact of emotion on physical problems and delay or exclude the possibility of psychological help. It was decided that all patients should be assessed by all professional disciplines at the beginning of their care so that the various issues could be identified and if appropriate, managed early on in the course of treatment. All patients then recognized that we were completing careful assessments, psychological and physical, and were less likely to be reluctant. Over 4 years ago we began a series of planning meetings to find the best way of incorporating multidisciplinary assessment at the commencement of care for all new patients of the Nova Scotia Environmental Health Centre. The outcome of these planning meetings was the introduction of the multidisciplinary assessment following the initial consultation by a physician at the centre. The revised care management scheme is outlined in the following paragraph. Figure 1 shows a schematic of the Nova Scotia Environmental Health Centre care model for complex and chronic conditions. The initial consultation lasts for one and a half hours and much information is gathered. The physician develops a problem list and identifies the various diagnoses that can be made. Recommendations are made which include whether the patient should return to the centre for a multidisciplinary assessment. This decision is not based upon a particular diagnosis, but rather on whether the patient has a chronic illness and clinical features which support the presence of central sensitivity (Yunus 2008). Most patients seen have a diagnosis of multiple chemical sensitivity often in association with fibromyalgia or chronic fatigue syndrome. Some patients have evidence of some new sensitivities but the major problem is not multiple chemical sensitivity rather fibromyalgia or chronic fatigue syndrome. There are an increasing number of patients who are ill, often enough to be disabled from work, where the question is asked if their illness is related to the environment, and who do not fulfill the consensus criteria for multiple chemical sensitivity, chronic fatigue syndrome or fibromyalgia. Such a person is referred for multidisciplinary assessment since it is clear that they are disabled and we conclude that they may well benefit from this approach to management.

At the time of the initial interview the patient has completed the detailed 217 item questionnaire, and is then asked to complete a one week dietary record and a two week record of activity (measured by a pedometer) in which they also record sleep pattern, pain level and fatigue level. They return for a morning in which they are seen by the various health professionals – nurse, dietician, psychologist or psychotherapist, coordinator of rehabilitation and occupational therapist (initially the team included a physiotherapist). The team meets together to discuss findings, interpretations and recommendations for treatment following completion of the assessments. A set of recommendations are agreed upon and the physician then meets with the patient to discuss further treatment. During this interview recommendations may change as the availability of the patient and other circumstances become clear.

The treatment plan depends upon the patient's willingness to learn self-management and to make necessary changes to restore health. Even though most patients are ill enough to seek medical help, and about half are so disabled that they have to stop work, it may take some time for an individual to accept that they have a significant illness and that they need to change. Old habits are hard to break and for some patients unhealthy life style habits such as smoking or heavy alcohol consumption need to be addressed at the outset. When there

are other clear stressors such as a poor diet or excessive consumption of cola drinks or caffeine containing beverages this is often the focus, and the dietician plays a major role in care early on. Patients may also require guidance on pacing their activities, this is apparent from the records which each patient has completed. Other recommendations depend upon the most prominent features.

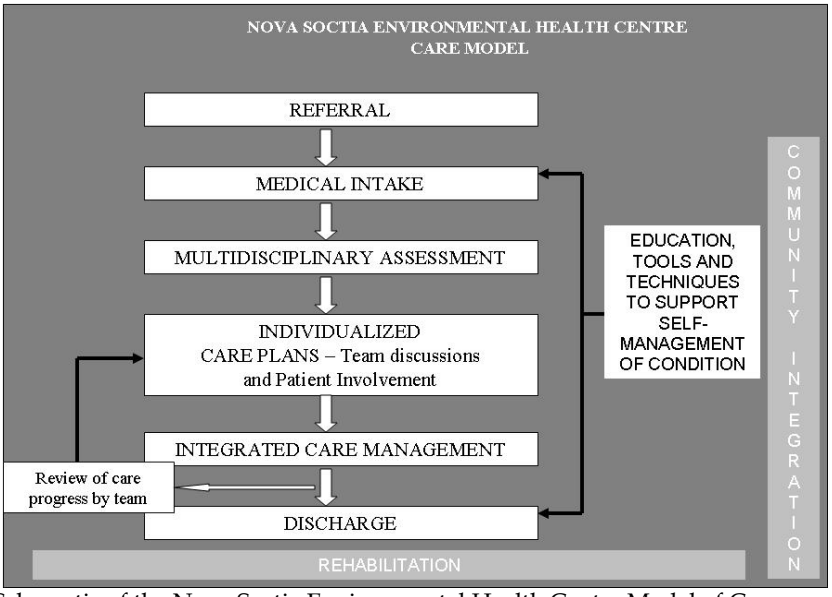

Fig. 1. Schematic of the Nova Scotia Environmental Health Centre Model of Care

If the patient is disabled and unable to work then proof of disability is often the highest priority. This can be most challenging when objective findings are not present. In this situation initial management at the Nova Scotia Environmental Health Centre may be in confirming the presence of environmental sensitivity by objective testing (Joffres et al 2005) and providing evidence of impaired functional capacity – if possible with a formal functional capacity evaluation by a professional familiar with this type of health problem.
Once the treatment plan is developed and the individual problems are addressed we are left with ill, disabled patients who are prepared to make changes to gain better health and return to work. Since our goal is to alleviate suffering we have created an environment to favour self-healing. We seek to foster salutogenesis (the creation of health) and decrease the impact of pathogenesis (the creation of suffering or disease). The salutogenic theory was proposed by Anton Antonovsky (1979). Antonovsky proposed that in managing chronic disease the emphasis should be to encourage movement towards health, and that a major consideration in health promotion needs to be enhancement of what he refers to as a sense of coherence(Antonovsky 1996). Our approach initially developed as we learned that many factors contributed to the illnesses that our patients experienced and if we were to alleviate suffering we needed to address these various aspects. As we have learned more of the nature of these illnesses the rationale or scientific underpinning of our approach has been validated.

7. Results of multidisciplinary assessment

By emphasizing the integration of mind and body and by introducing psychosocial assessment at the same time as detailed physical/biological assessments, we are able to focus our therapeutic efforts in the most appropriate area. All patients need help in reducing contaminants – whether from the outer (environmental stress) or inner (emotional) environments. The balance of emphasis varies between patients and this can be determined early on in the course of management.

At the time of introducing multidisciplinary assessments for all patients who were to receive treatment at the centre, we decided to follow progress in a variety of ways. Each program is evaluated through research to measure treatment efficacy. In addition, each patient completed the 217 item questionnaire at the time of initial consultation. Each patient also completed the NSEHC-BREF questionnaire (Fox et al 2008) after 6 months of treatment, after 1 year and after 2 years. The same patients have been followed throughout . In this section, the results from a group of 250 patients who went through the multidisciplinary assessments are presented.

Period of time follow up	6m-1yr (n=250)			1 – 2 yr (n=153)			2+ yr (n=65)		
	Pre Mean (SD)	Post Mean (SD)	p-value	Pre Mean (SD)	Post Mean (SD)	p-value	Pre Mean (SD)	Post Mean (SD)	p-value
Rating of health since onset of illness	3.52 (1.2)	4.22 (1.5)	0.05	3.64 (1.2)	5.35 (1.4)	<0.0001	3.45 (1.2)	5.4 (1.2)	<0.0001
Limitation contact with people to avoid exposures	2.75 (1.1)	1.82 (1.2)	0.02	2.88 (1.1)	1.7 (1.2)	0.01	2.72 (1.1)	1.9 (0.9)	0.02
Feel too ill to do housework	3.6 (0.8)	3.1 (1.2)	0.05	3.45 (0.8)	2.8 (1.01)	0.001	3.82 (1.02)	2.5 (1.1)	0.002

Table 1. Changes measured in overall health in patients who received multi-disciplinary assessments at commencement of treatment

Since the original study using the NSEHC-BREF the major change that has occurred has been the introduction of the multidisciplinary assessment. The population of patients is similar and the main programs of treatment have remained the same. The results before and after introduction of the multidisciplinary process have been compared.

Period of time in follow up	6 mth – 1 yr		1 -2 years		More than 2 years	
	Pre-	Post	Pre-	Post	Pre-	Post
Pre-Multi-disciplinary assessment	2.9	3.03	3.5	3.1	3.5	3.3
Post-Multi-disciplinary assessment	2.75	1.82	2.88	1.7	2.72	1.9

Table 2. Pre- and Post-introduction of Multidisciplinary assessment – Question 2. Limit contact with other people to avoid exposure

Two hundred and fifty patients have completed the NSEHC-BREF questionnaire between 6 and 1 year, 153 have completed the questionnaire between 1 and 2 years and 65 have now gone beyond 2 years. The length of treatment and the specific type of therapy varies but the results are of great interest.

In the first study (pre-assessments), the patients were different in each group and this is reflected in the variation in the initial score, prior to treatment as shown in Table 2. There was no significant change after treatment at 6 months or 1 year. Only at 2 years did the change reach statistical significance (p-value 0.02). In the post-multidsiciplinary assessment set of results, the changes across time periods are captured in the same group of patients. The variation in the pre scores is due to the changes in the sample size at the three time periods. In contrast to the pre-assessment results, the reduction of this symptom was statistically significant for each of the 3 time periods. This is a significant difference in this patient population which demonstrates that chemically sensitive patients learned faster to cope with being sensitive and did not perceive the same need to limit contact with others to reduce chemical exposures. It would appear that from the outset, the patients experience some gains in health that changes their behaviour. This needs further exploration.

Looking at the 8 questions pertaining to irritative symptoms in the eyes and respiratory system, the changes are comparable between the two studies. The results for the patients seen after the introduction of assessments are shown in Table 3. In the 2 year group, there were only 65 patients and for the symptoms of burning eyes there was no improvement seen. In the previous study, (Fox et al 2008) there were 118 patients in this group and this symptom had improved at 2 years (p value 0.05). The improvement in question 2 was similar and reached significance at 2 years (p-value <0.0001) for the pre-assessment patients. It can be seen in Table 3 that this symptom showed significant improvement in all of the post-assessment groups. All other questions were comparable, showing similar changes in the same time periods.

In the post-assessment group, all of the questions which asked about more generalized symptoms – namely difficulty in concentrating, forgetfulness or poor memory, feeling light headed, irritability, tiredness not relieved by sleep, fatigue or very tired without energy and muscle pain or ache not related to exercise showed significant improvement in the first cohort between 6 months and 1 year (Table 4). In contrast, the follow up study prior to the introduction of the assessment process did not show the same degree of improvement. There was no significant change in the first time period (6 months to 1 year) in four of the questions in this cohort – namely forgetfulness; irritability; fatigue or very tired without energy; and muscle pain, ache without exercise.

Question	6m-1yr (n=250)			1 – 2 yr (n=153)			2+ yr (n=65)		
	Pre Mean (SD)	Post Mean (SD)	p-value	Pre Mean (SD)	Post Mean (SD)	p-value	Pre Mean (SD)	Post Mean (SD)	p-value
Burning eyes	2.8 (2.1)	2.7 (2.2)	0.7	3.1 (2.7)	2.9 (2.5)	0.4	3 (3.2)	2.6 (2.5)	0.07
Itchy eyes	2.15 (2.4)	1.22 (1.5)	0.0008	3.2 (3.8)	2.33 (2.3)	0.0009	2.5 (2.3)	1.01 (1.4)	<0.0001
Stuffy or full sinuses	5.2 (4.9)	4.7 (3.5)	0.9	5.1 (4.9)	3.3 (3.7)	0.008	5.4 (5.6)	2.8 (2.4)	<0.0001
Stronger sense of smell	3.95 (3.3)	2.35 (2.5)	0.08	4.2 (3.8)	2.2 (1.9)	0.02	3.5 (2.8)	1.6 (1.1)	0.03
Usually acceptable odours were sickening	4.8 (3.5)	4.4 (3.6)	0.4	5.2 (4.6)	4.5 (3.7)	0.09	4.9 (4.1)	3.1 (3.5)	0.01
Tight chest	2.6 (1.9)	1.1 (1.8)	0.01	3.5 (3.1)	1.3 (1.7)	0.0006	2.5 (1.6)	1.5 (1.2)	<0.0001
Hoarse or loss of voice	2.7 (1.9)	2.2 (1.3)	0.5	3.2 (2.4)	2.6 (3.2)	0.5	2.9 (3.5)	1.3 (1.1)	<0.0001

Table 3. Changes in symptoms in eyes, nose, throat and respiratory systems

8. Emergence of interdisciplinary care

As the various health professionals have worked together in an increasingly integrated fashion it has become clear that timely and relevant collaborative care management is important to deliver seamless care for individuals with complex health conditions such as multiple chemical sensitivity. The consistent themes of self-management and self awareness or mindfulness are introduced early on in the care. The core principles of support and education for a patient reinforced by all health professionals include raising awareness of one's capacity, pacing of activities, healthy lifestyle choices and maintaining a balance between avoidance of situations that trigger symptoms and engaging in life which inevitably brings environmental and other stresses . We reinforce the need to be aware of body signals and introduce techniques to reduce high levels of arousal in the nervous system. Members of the health care team try to model this balance in their treatment strategies to encourage reduced arousal. Different health professionals work together to deliver educational programs and workshops, for example mindfulness is the basis for a nutritional workshop entitled "Mindful eating". We meet regularly to ensure that our

approaches support one another and more importantly assist the patient in moving towards health. We foster an environment of trust and of hope but at the same time of recognizing what our limitations are and that not all illnesses and disease can be fully alleviated. If disability persists, then it needs to be accepted. It is still possible to move along the continuum between health and disease, towards health – particularly as concepts of what it means to be healthy shift. In this way the management has become interdisciplinary.

Period of time follow up	6m-1yr (n=250) Pre Mean (SD)	Post Mean (SD)	p-value	1 – 2 yr (n=153) Pre Mean (SD)	Post Mean (SD)	p-value	2+ yr (n=65) Pre Mean (SD)	Post Mean (SD)	p-value
Difficulty concentrating	5.0 (4.9)	3.1 (2.5)	0.01	5.8 (4.6)	2.8 (2.4)	0.0002	6.2 (3.5)	2.9 (2.3)	<0.0001
Forgetfulness / poor memory	3.2 (2.8)	1.7 (1.5)	0.004	4.6 (3.3)	2.1 (2.5)	0.0009	4.9 (4.1)	1.2 (1.4)	<0.0001
Feeling light headed	4.4 (3.3)	2.3 (2.1)	0.05	4.8 (3.9)	2.1 (2.8)	0.009	5.9 (5.7)	2.5 (2.1)	<0.0001
Irritability	3.2 (3.1)	1.3 (2.6)	0.07	3.5 (2.4)	1.4 (1.3)	0.04	3.8 (2.4)	1.2 (1.1)	<0.0001
Tiredness not relieved by sleep	7.2 (4.8)	4.5 (3.1)	0.004	7.9 (5.2)	4.9 (2.5)	0.003	6.5 (4.2)	2.9 (2.5)	0.0001
Fatigue, very tired, without energy	5.9 (3.1)	3.2 (1.9)	0.0001	5.4 (3.5)	2.1 (1.8)	0.0002	6.2 (5.4)	1.3 (1.1)	<0.0001
Muscle pain or ache not related to over exercise	4.8 (2.9)	2.9 (1.4)	0.03	4.5 (2.6)	2.1 (1.4)	0.004	4.1 (3.5)	3.7 (1.1)	0.2

Table 4. Changes measured in blood/gland, muscle, joints and nervous system

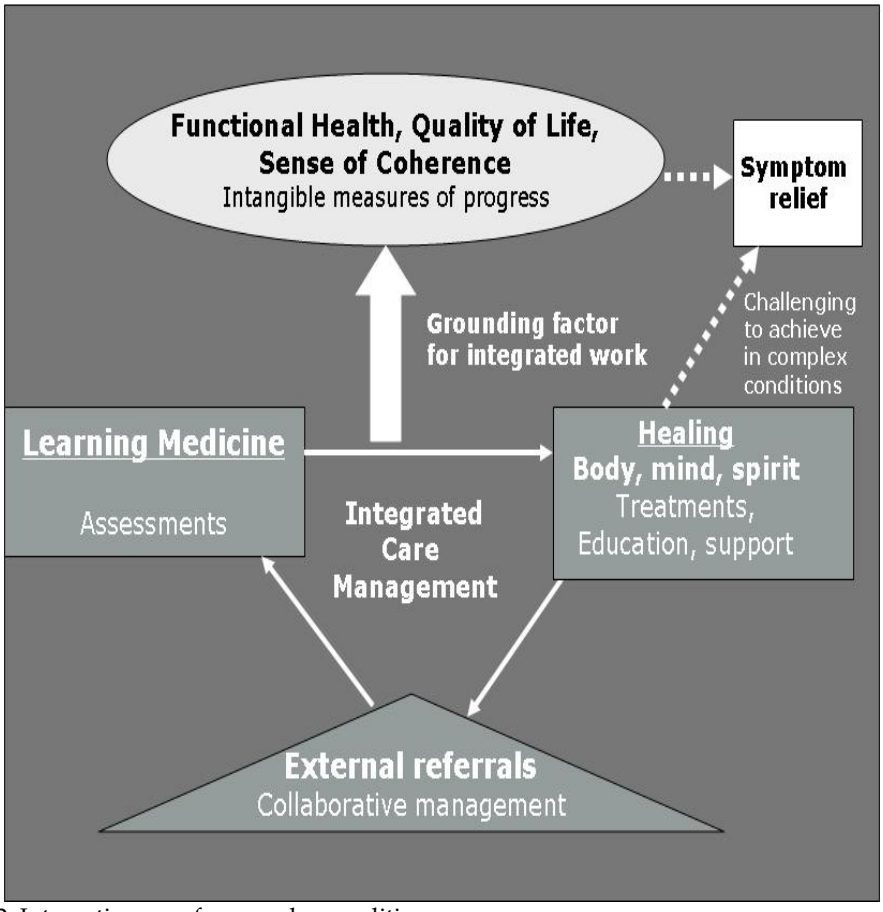

Fig. 2. Integrating care for complex conditions

In working together as a team, each individual brings their unique skills and perspectives to focus on particular problems and treat different aspects. The focus of each clinican may be upon one particular symptom at one time. At the same time, the collective focus needs to be on improved quality of life for the patient, through better function. The need to maintain this goal of increased coherence towards salutogenesis has become more apparent with time and will be part of our continued development as a team. The principles are represented schematically in Figure 2.

The adoption of a patient –centred approach to management is consistent with the evidence that already exists in the medical literature that there is great variability between patients.Various subgroups have been identified in patients diagnosed with fibromyalgia (Turk et al 1998, Giesecke et al 2003, Harris et al 2005) and treatment outcomes vary between the different sub-groups (Turk et al 1998).

The various conditions that are seen at Nova Scotia Environmental Health Centre share a common characteristic and that is central sensitivity (Yunus 2008). Central sensitivity has

been objectively confirmed in fibromyalgia, irritable bowel syndrome and temporo-mandibular problems. Our clinical experience allows us to postulate that the same phenomenon exists in patients with multiple chemical sensitivity. The physiology of central sensitivity is activation of nociceptors of the A-delta and C fibers at the peripheral tissues by bradykinin, serotonin, prostaglandins and substance P. This follows inflammation that may be caused by even minor trauma. A variety of changes cause an escalation of hyperexcitability of second-order neurons, giving rise to hypersensitivity to various peripheral stimuli. When pain results it can be enhanced by emotion and selective attention. It is clear that other factors are likely to affect central sensitvityy namely genetics, sympathetic overactivity, endocrine dysfunction, viral infection, peripheral nociceptor generators like arthritis, poor sleep, environmental stimuli like weather, noise and chemicals, trauma and psychosocial distress. It is hoped that with time we will gain a better understanding of these issues and move further upstream to prevent descent into ill health. Our approach which developed over several years addresses these various issues. We have shown that improvement in an individual's ability to manage their own health problems accompanies reduction of symptoms. Clearly the earlier that each person can learn what is important in fostering health, the more likely it is that health is maintained and disability reduced.

Many of our quality and research intiatives are aimed at improving the collaborative environment among multidisciplinary clinicians that are involved in the care management of patients. These initiatives include revision of the Centre's care model, standardizing clinical assessements and exploring semantic interoperability to the multidisciplinary clinical vocabulary (Sampalli et al 2010). The Centre's revision of the care model shown in figure 2, is geared towards shifting the focus of the care team into a layer of modelling a patient's health above the level of symptom management. In the new model, the functioning of the care team will be integrated around more meaningful outcomes such as coherence, quality of life and function. The primary objective of this shift is to center the care team's efforts towards the salutogenic approach of enabling self-efficacy and coherence in patients. The Centre's efforts will also continue towards standardizing clinical vocabulary and assessment tools used by the multidisciplinary clinicians in order to facilitate a higher level of shared understanding and coherence in the collaborative functioning of clinicians.

9. Conclusion

The limited treatment options and the inability for most patients to find any kind of effective medical treatment lead to the establishment of the Nova Scotia Environmental Health Centre. The multidisciplinary approach grew out of the recognition of the complex interactions that span multiple health dimensions and appear to govern the well-being of individuals with this illness; and the ineffectiveness of uni-dimensional treatment models in addressing the multitude of symptoms. It soon became clear that improving health of both body and mind alleviated suffering and reduced disability.

The care model for a complex chronic illness discussed in this chapter focuses on multiple chemical sensitivity. The findings reported here are undoubtedly relevant to other complex, chronic illnesses of uncertain etiology when there is often limited understanding of pathogenesis. We have shown that poorly understood chronic medical conditions which result in significant health care costs and disability can be helped by an interdisciplinary approach which focuses on movement to health – salutogenesis rather than pathogenesis.

10. References

Abbass , A.; Kisely, S. & Kroenke, K. (2009). Short-term psychodynamic psychotherapy for somatic disorders. Systematic review and meta-analysis of clinical trials. *Psychother Psychosom* 78.(May 2009) 265-274.

Antonovsky, A. (1979). *Health stress and coping*. Jossey Bass, San Francisco.

Antonovsky, A. (1996). The salutogenic model as a theory to guide health promotion. *Health Promotion International* Vol. 11 (Jan 1996) 11-18.

Banic, B.; Petersen-Felix, S.; Andersen, O.K.; Radanov, B.P.; Villiger , P.M. & Arendt-Nielsen, L. (2004). Evidence for spinal cord hypersensitivity in chronic pain after whiplash injury and in fibromyalgia. *Pain* 107. 7-15.

Bartha, L.; Baumzweiger, W., Buscher, D.S. et al (1999) Multiple chemical sensitivity: a 1999 consensus. *Arch Environ Health* Vol. 54 (May-Jun 1999) 147-149.

Binder, L.M. (2004). Medically unexplained symptoms and neuropsychological assessment. *J Clin Exp Neuropsychol* 26. 369-392.

Caress, S.M. & Steinemann, A.C. (2004) . A national population study of the prevalence of multiple chemical sensitivity. *Arch Environ Health* 59, 300-305.

Carson, A.J.; Ringbauer, B.; Stone, J.; McKenzie, L.; Warlow, C. & Sharpe, M. (2000). Do medically unexplained symptoms matter? A prospective cohort study of 300 new referrals to neurology outpatient clinics *J Neurol Neurosurg Psychiatry* 68. 207-210.

Childre, D. & Martin, H.(1999). *The HeartMath Solution* HarperCollins, New york, NY.ISBN 978-0-06-251606-0

Coffin, B.; Bouhassira, D.; Sabate, J-M.; Barbe, L. & Jian, R. Alteration of the spinal modulation of nociceptive processing in patients with irritable bowel syndrome. *Gut* 53. 1465-1470.

Cone, J.E. & Sult, T.A. (1992). Acquired intolerance to solvents following pesticide/solvent exposure in a building: a new group of workers at risk for multiple chemical sensitivities? *Toxicol Ind Health* 8. 29-40.

Cullen, M. (1987). The worker with multiple chemical sensitivities: an overview. *Workers with multiple sensitivities, Occupational Medicine: State of the Art Reviews. Cullen M.* (Ed.) 2. 655-662. Hamley and Belfus, Philadelphia.

Davidoff, A.L. & Fogarty, L. (1994). Psychogenic origins of multiple chemical sensitivities syndrome: a critical review of the research literature. *Arch Environ Health* Vol. 49 (May 1994) 316-325.

Davidoff, A.L.; Keyl, P.M. & Meggs W. (1998). Development of multiple chemical sensitivities in laborers after gasoline fume exposure in an underground tunneling operation. *Arch Environ Health* 53. 183-189.

de Figueiredo, J.M. (1980). Briquet's syndrome in a man with chronic intractable pain. *John Hopkins Med J* 147. 102-106.

Desmeules, J.A.; Cedraschi, C.; Rapiti, E.; Baumgartner, E.; Finckh, A.; Cohen , P.; Dayer, P. & Vischer, T.L. (2003) Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. *Arthritis Rheum* 48. 1420-1429.

Fink, P. & Rosendal, M. (2008) Recent developments in the understanding and management of functional somatic symptoms in primary care. *Curr Opin Psychiatry* Vol.21 (2008) 182-188.

Ford, C.V. (1997). Somatization and fashionable diagnoses: illness as a way of life. *Scand J Work Environ Health* Vol. 23 (suppl.3 1997) 7-16.

Fox, R.A.; Sabo, B.M.T.; Williams, T.P.W.; Joffres. M.R.; (1999) Intradermal testing for food and chemical sensitivities. J Allergy Clinical Immunology Vol 103 (May 1999) 907-911.

Fox, R.A.; Joffres, M.R.; Sampalli, T. & Casey, J. (2007). The impact of a multidisciplinary, holistic approach to management of patients diagnosed with multiple chemical sensitivity on health care utilization costs; an observational study. *J Altern and Comp Med* 13. 223-229.

Fox, R.A.; Sampalli, T. & Fox , J. (2008). Measuring health outcomes of a multidisciplinary care approach in individuals with chronic environmental conditions using and abbreviated symptoms questionnaire. *J Multidisciplinary Healthcare* 1. 97-104.

Giesecke, T.; Williams, D.A.; Harris, R.E.; Cupps, T.R.; Tian, X.; Tian, T.X. (2003) Subgrouping of fibromyalgia patients on the basis of pressure-pain thresholds and psychological factors. *Arthritis Rheum* Vol. 48 (2003) 2916-2922.

Gyntelberg, F.; Vesterhauge, S.; Fog, P.; Isager, H. & Zillstorff, K. (1986). Acquired intolerance to organic solvents and results of vestibular testing. *Amer J Ind Med* 9. 363-370.

Harris, R.E.; Williams, D.A.; McLean, S.; Sen, A.; Hufford, M. (2005) Characterization and consequences of pain variability in individuals with fibromyalgia. *Arthritis Rheum* Vol.52 (2005) 3670-3674.

Henningsen, P.; Zimmerman, T. & Sattel, H. (2003). Medically unexplained physical symptoms, anxiety, and depression. *Psychosom Med* 65:528-533

Jason, L.A.; Richman, J.A.; Rademaker, A.W.; Jordan, K.M.; Pliopys, A.V.; Taylor, R.R.; McCready, W.; Huang, C.F. & Pliopys, S. (1999). A community-based study of chronic fatigue syndrome. *Arch Intern Med* Vol. 159 (1999) 2129-2137.

Joffres, M.R.; Williams, T.; Sabo, B. & Fox, R.A. (2001). Environmental sensitivities: Prevalence of major symptoms in a referral center; The Nova Scotia Environmental Sensitivities Research Center Study. *Environ Health Perspect* 109. 161-165.

Joffres , M.R.; Sampalli, T. & Fox, R.A. (2005). Physiologic and symptomatic responses to low-level substances in individuals with and without chemical sensitivities: a randomized controlled blinded pilot booth study. *Environ Health Perspect* 113. 1178-1183.

Kabat-Zinn, J. (1990). *Full catastrophe living: using the wisdom of your body and mind to face stress, pain and illness.* Dell publishing. New York, NY.

Kabat-Zinn, J.; Massion, A.O.; Kristeller, J.; Petersen, L.G.; Fletcher, K.E.; Pbert, L.; Lenderking, W.R. & , Santorelli, S.F. (1992). Effectiveness of a meditation-based stress reduction program in the treatment of anxiety disorders. *Amer J Psychiatry* 149. 936-943.

Kretzer, R.; Neutra, R.R. & Lashuay, N. (1999) Prevalence of people reporting sensitivities in a population based survey. *Amer J Epidem Vol.* 150 (1999) 1-12.

Kroenke, K.(2006) Physical symptom disorder: a simpler diagnostic category for somatization-spectrum conditions. *J Psychosom Res* Vol.60 335-339.

Manu, P (1998) *Functional somatic syndromes: etiology, diagnosis and treatment.* Cambridge University Press, Cambridge.

McCraty, R.; Barrios-Choplin, B.; Rozman, D.; Atkinson, A.; Watkins, A. (1998). The impact of a new emotional self-management program onstress, emotions, heart rate variability, DHEA and cortisol. *Integrative Physiological and Behavioral Science* Vol.33 (Feb 1998) 151-170.

Nethercott, J.R.; Davidoff, L.L.; Curbow, B. & Abbey, H. (1993) Multiple chemical sensitivities syndrome: toward a working definition. *Arch Environ Health* Vol. 48 (Jan 1993) 19-26

Nettleton, S. (2006). "I just want permission to be ill": towards a sociology of medically unexplained symptoms. *Soc Sci Med* 62. 1167-1178.

Reyes , M.; Nisenbaum, R.; Hoaglin, D.C.; Unger, E.R.; Emmons, C.; Randall, B.; Stewart, J.A.; Abbey, S.; Jones, J.F.; Gantz, N.; Minden, S. & Reeves, W.C. (2003) Prevalence and incidence of chronic fatigue syndrome in Wichita, Kansas. *Arch Int Med* Vol.163 (2003) 1530-1536.

Rockwood, K.; Fox, R.A.; Stolee, P.; Robertson, D.; Beattie, B.L. (1994). Frailty in the elderly: an evolving concept. *Can Med Assoc J* Vol.150 (4, 1994) 489-495

Rockwood, K.; Mogilner, A; Mitnitski, A. (2004). Changes with age in the distribution of the Frailty Index. *Mech Ageing Develop* Vol.125 (June 2004) 517-519.

Sampalli, T.; Berlasso, E.; Fox, R. & , Petter M. (2009). A controlled study of the effect of a mindfulness-based stress reduction technique in women with multiple chemical sensitivity, chronic fatigue syndrome and fibromyalgia. *J. Multidisciplinary Healthcare* 2. 53-59.

Sampalli, T.; Shepherd, S.; Duffy, J. & Fox, R. (2010). An evaluation of SNOMED CT in the domain of complex chronic conditions. *Int. J of Integr Care* March 24. 10.

Schoen , C.; Osborn, R.; How, S.K.H.; Doty, M.M. & Peugh, J (2008). In Chronic Condition: experiences of patients with complex health care needs, in eight countries, 2008. Health Affairs (Project Hope) 28, 1

Smythe, H.A. (2005). Temporomandibular joint disorder and other medically unexplained symptoms in rheumatoid arthritis, osteoarthritis, and fibromyalgia. *J Rheumatol* 32. 2288-2290.

Stockl, A. (2007). Complex syndromes, ambivalent diagnosis and existential uncertainty: the case of systemic lupus erythematosus (SLE) *Soc Sci Medicine* Vol.65 (2007) 1549-1559.

Tabershaw, I.R. & Cooper, W.C. (1966). Sequelae of acute organic phosphate poisoning. *J Occup Med* 8. 5-20.

Turk, D.C.; Okifuji, A.; Sinclair, J.D.; Starx, T.W. (1998) Differentail responses by psychosocial subgroups of fibromyalgia syndrome patients to an interdisciplinary treatment. *Arthritis Care Res* Vol.11 (1998) 397-404.

Verhaak, P.F.& Meijer, S.A.; Visser, A.P. & Wolters, G. (2006) Persistent presentation of medically unexplained symptoms in general practice. *Fam Pract.* **23**:414–420.

Yunus, M.B. (2000). Central sensitivity syndromes: a unified concept for fibromyalgia and other similar maladies. *J Indian Rheum Assoc* 8. 27-33.

Yunus, M.B. (2007). Fibromyalgia and overlapping disorders; the unifying concept of central sensitivity syndromes. *Semin Arthritis Rheum* 36. 335-356.

Yunus, M.B. (2008). Central sensitivity syndromes: a new paradigm and group nosology for fibromyalgia and overlapping conditions, and related issue of disease versus illness. *Semin Arthritis Rheum* 37. 339-352.

3

Pain experience and expression in patients with dementia

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Up to 2025 1.2 billion people are going to be aged 60 and more (Fine, 2009). In USA individuals aged 85 and older are the fastest growing segment of population which is expected to double until 2030 (Evers et al., 2002; Mantyselka et al., 2004). Pain is an inseparable companion of the old age. The aim of the chapter is to describe the issues of pain presence in the population of the elderly with dementia from the theoretical and clinical point of view.

We can characterize it as an unpleasant sensory and emotional sensation related to actual or potential tissue damage or described in terms of such damage (International Association for the Study of Pain, 2008). According to another definition pain is a compound, subjective phenomenon comprising nociceptive, perceptive, cognitive and emotional factors (Melzack and Wall, 1965; Cipher & Clifford, 2004). There are two main kinds of pain distinguished – acute and chronic one (Leone et al., 2009). The acute pain accounts for an essential defense mechanism which emerges in a situation of an organic or traumatic injury and its goal is to prevent the further damage increase. The chronic pain is more difficult to define because there are no clear time limits which would enable to assert when acute pain turns into chronic one. Generally it is assumed that pain, that remains longer than an expected healing time, is found to be the chronic one. Rouhgly speaking the minimum time span required for a diagnosis of chronic pain is estimated for 6 – 8 weeks (Mersky, 1986; Leone 2009) or 1 – 3 months (Sawyer et al., 2007).

Torvik et al. (2010) claims that pain is the main problem in nursery homes and an estimated frequency of its prevalence is between 27% and 84%. Similar data are quoted by Manfredi et al. (2003) who claims pain and dementia are common in nursery homes with prevalence rates of 45%-84% and 40%-78% respectively. Fries et al. (2001) reports that 68% of nursery homes residents suffers from any kind of pain. Teno et al. (2001) speaks about a range of 40% - 46% of residents experiencing pain and according to Snow's et al. (2004) estimates – 67,4%. Horgas et al. (2009) pertaining to elderly population in general states that pain is an experience shared by 50% - 86% of them.

Individuals with dementia also often suffer from pain – according to Horgas et al. (2009) this problem touches every day 32% to 53% of this group. Older research estimate prevalence of pain in the patients with dementia living in nursery homes at 60%-90% of the population (Krulewitch et al., 2000; Parmelee et al. 1993; Ferrell et al., 1990; Ferrell et al., 1995; Shega et al., 2004). There are data quoted in the literature suggesting pain prevalence in 33% to 80%

patients with dementia (Brummel-Smith et al., 2000). Shega in his research states that thirty two percent of individuals with dementia declare experiencing pain in the present moment. Among them 65% talk about slight pain, 27% about moderate and 8% about severe. Moreover, 52% of their caregivers claim that they feel some pain at the present moment, 52% talk about light pain, 30% about moderate one and 18% about severe one (Shega et al., 2004). Despite the above mentioned frightening statistics, the quoted authors in another research proved that risk of insufficient analgesia was 1.07 higher for every additional year of life, 3.0 higher if a patient suffered from dementia and 2.5 higher if a patient demonstrated impairments of activities of daily life (Shega et al., 2006). Generally, it should be stated that a level and frequency of pain prevalence in individuals with dementia are definitely underestimated (Reynolds et al., 2008; Cohen-Mansfield, 2002; Cornali et al., 2006).

What are the causes of such underestimation of pain intensity in the elderly population, especially in ones with dementia, and of insufficient counteracting it (Herr, et al., 2006)? Attitudes of the elderly, of medical staff and some research results contribute to this situation. According to Torvik et al. (2010) the elderly may reveal reluctance or not be able to complain about pain and, moreover, they may have a reduced ability to understand experienced pain and to convey this experience. Miaskowski (2000) points at more social reasons of decreased informing about pain by elderly individuals – they may meet negative attitudes of caregivers in a response to such behaviors. Furthermore, they may also assume that pain is an expected aspect of aging and due to this fact there is no reason to mention about it (Sawyer et al., 2007). Finally, lack of expected help from others may incline the elder persons to resign from complaining about it to the environment. An elderly's ability to communicate is of great importance. Sengstaken & King (1993) proved that physicians could identify pain in 43% of communicative patients and in only 17% of those who could not communicate.

Schuler et al. (2007) analyzing the causes of insufficient analgesia, which may be associated with characteristics of medical staff, states similarly to above mentioned Miaskowski, that both, personnel and residents share an opinion, that pain at the old age is a natural element of the human existence and has to be accepted because there is nothing that could be done about it. One of the consequences of such a belief is lack of sufficient attention paid to elderly's complaints on pain by nurses. Apart from it, medical staff does not have sufficient skills of pain recognition which expression may be often altered what is going to be a topic of discussion later (Zwakhalen et al., 2007). Cook et al. (1999) takes notes of too small employment of available pain assessment scales. Weissman et al. (2001; Weismann & Matson, 1999) emphasize difficulties associated with conditions prevalent at nursery homes: rare presence of physicians, shifting the burden of responsibility for direct care to not qualified enough nurses and resulting from such a situation defiance against employment of analgesics associated with a fear of administrative control.

Research results suggesting that the elderly better endure pain than the young and middle-aged adults and that they declare higher quality of life, may be another source of lesser paying attention to pain in the elderly (Torvik et al., 2010). Whereas Gibson & Helmer (2001) state that age of an individual is a cause of a decreased ability to perceive pain and communicate it. Reports proving something completely opposite should be noted – e.g. Fine (2009) claims that aging can lead to pain sensitivity increase with concurrent changes in absorption, bioavailability and medications absorbing time what may only increase

suffering. Similarly Kamel et al. (2001) states that there has been no physiological changes in the elderly found, that could influence pain perception. Indeed, people at the old age may experience more pain than younger ones (Kwentus et al., 1985) but be less prone to complain about it (Melding, 1991). With regard to this fact it should be especially kept in mind that the elderly often declare experiencing pain of less intensity than they actually feel (Ferrell et al., 1995).

Individuals with dementia are in a particularly disadvantageous situation. As Nygaard & Jarland (2005) claim, a label of dementia may distort interpretation of pain signals in patients with this disorder, what is related to lesser analgesics employment. Reynolds et al. (2008) found, that pain documentation decreased linearly with increase of a degree of cognitive impairments. Individuals without such impairments or with its mild form had higher probability of mild or severe pain recognition, while pain experienced by less cognitively efficient individuals was more often classified as mild one. Consequently, according to the authors, the higher degree of cognitive impairments, the lower probability that a patient will obtain analgesic treatment: 80% of cognitively intact residents received analgesics, while similar procedures covered only 56,2% of patient with severe impairments ($P<0.001$). Results obtained by Morrison & Siu (2000) approve that the problem may be an effect of communication difficulties not differences in experiencing. In the research on treatment of patients after a hip fracture – a condition independent from a level of cognitive efficiency – the authors found that individuals with dementia received one third of morphine derivatives prescribed to cognitively intact people. Brummel-Smith et al. (2002) also proved that patients with dementia were more rarely given analgesics (14% of the investigated group vs. 31% of the cognitively intact; $p<0,006$) and that an average time span of analgesics application was shorter (1,6 month vs. 2,9 months respectively). Moreover, Gruneir et al. (2006) also points that patients with dementia are more rarely visited by physicians and the visits times are shorter. Findings of Cohen-Mansfield & Lipson (2002) stating that cognitive status is a more important predictor of pain assessment carried out by a geriatrician than the diagnosis itself related to the pain. Furthermore, the authors note a stable trend to perceive a lower level of pain in patients with severe dementia regardless of pharmacological treatment employed to its relief.

Cook et al. (1999) mentions four causes of underestimation of pain in individuals with cognitive impairments:

- the elderly's habits associated with communicating their condition,
- a degree of acceptance of this information by medical staff,
- caregivers' skills to recognize pain,
- inadequacy of available tools for pain assessment with relation to capabilities of individuals with cognitive impairments.

It should be stated that, despite existing results suggesting that individuals with dementia can reliably communicate their pain (e.g. Parmelee et al., 1993), medical personnel does not trust relations of people under their care (Sengstaken & King, 1993). Perhaps, it is partially associated with a conviction that dementia, as a neurological disorder, may affect pain experiencing by central nervous system and cause disintegration of awareness of external painful stimuli (Reynolds et al., 2008). Moreover, other research results suggest, that more than one fifth of the elderly living in nursery homes can neither answer yes or no to a question, nor can independently communicate their condition (Ferrell et al., 1995; Parmelee et al., 1993). Marzinski (1991; Achterberg, 2007), however, claims that patients with

Alzheimer's disease show a lower level of pain than cognitively intact elderly. At this moment it is worth citing research results documenting that individuals with cognitive impairments experience similar pain as healthy controls do, and even, as it happens in case of some dementias, an increase of an affective component of the pain experience may be found (Scherder et al., 2003; Scherder et al., 2003). E.g. patients with vascular dementia may declare an increase of experienced pain (Manfredi et al., 2003; Ferrell et al., 1995). This issue is going to be discussed in a more detailed way later on.

What do we know about pain experiencing by patients with dementia? Lots of research results, especially older ones, suggest decreased ability to experience pain by this group of ill individuals. Recent reports, however, suggest that the above conviction may be rather an effect of an artifact associated with pain measurement methods. As it is underlined by some authors, most of the tools for assessment of experienced pain was developed on the basis of work with cancer patients and relies on a verbal report, what is a serious barrier in case of severe dementia (Morrison et al., 1998; Boyer et al., 2004). Bachino et al. (2001) states directly that there are no evidence proving, that individuals with dementia experience lesser pain – it seems rather that they have problem with its recognition and verbal communicating its presence. Although some researchers (Pautex et al., 2006; Stein & Ferrell, 1996; Hurley et al., 1992; Parke, 1998) suggest that individuals with dementia are able to inform about their state, more detailed studies indicate that a relationship between a number of pain complaints and a cognitive status measured with MMSE is inversely U-shaped. In initial phases of dementive process progression, the number of reports about pain experience increases, but later it starts to decrease (Merlino et al., 2002).

The topic literature is dominated by reports showing lesser prevalence of pain in population of individuals with dementia or at least higher tolerance of it. Healthy controls are compared with the ill ones, and different subtypes of dementia are compared, too. Thus, Parmelee (1996; Husebo et al., 2008) states that patients with severe dementia state less painful locations and lesser pain intensity than non-demented individuals. Leong & Nuo (2007) prove, that together with dementia progression, the amount of reported pain decreases. Similar results are obtained by Proctor & Hirdes (2001). On the other hand, other research (Scherder et al., 1999; Fisher et al., 2002; Zwakhalen et al., 2009) came to an end with a conclusion that a cognitive status does not affect pain prevalence. Blennow's et al. (1993) research results show, that cases of headache incidents as consequences of lumbar punction are scarce among patients with dementia, covering 2% of the procedure subjects, whereas in healthy elderly population they afflict about 40% of subjects. Husebo et al. (2008) compared pain experiences, their frequency and intensity in patients with different subtypes of dementia. He found that intensity of experienced pain did not differentiate the dementia groups. Instead they discovered that a number of painful locations in patients with vascular dementia (VaD) was bigger than in individuals with Alzheimer's disease. They explain it as a result of deafferentiation of VaD patients as a consequence of impairments of white matter, what is conducive to intensification of painful experiences (Scherder, Slaets & Deijen, 2003).

Researchers from the discussed domain differentiate an ability itself to experience pain and an ability to endure it. Benedetti et al. (1999; Benedetti et al., 2004) found, that patients with Alzheimer's disease have higher tolerance for pain in comparison with patients with other types of dementia and healthy elderly. These changes are visible at a neurophysiological level – an EEG pattern in patients with AD reveals an interesting relation: the slower EEG,

the higher pain tolerance (Benedetti et al., 1999). Porter et al. (1996) and Rainero et al. (2000) proved, that autonomic nervous system responses for painful stimulation are changed in this group of patients. Namely, employing electrical stimuli was associated with both decreased perception of them and reduced increase of heart rate and blood tension. Cole et al. (2006) found that patients with AD reveal higher amplitude and latency in fMRI in response to noxious stimuli in comparison with healthy controls.

Sensory-discriminative and affective-emotional components are often discussed in the literature (Benedetti et al., 2006; Benedetti et al., 1999, 2004; Achterberg et al., 2010; Scherder et al., 2001). The first one includes perception of a painful stimulus, the second one means an emotional reaction for this perception, the aspect of suffering. The quoted authors say that in Alzheimer's disease the second component is impaired while the first one keeps stable, what results in a fact that patients with dementia can differentiate between painful and haptic stimuli (Benedetti et al., 1999; Gibson et al., 2001b; Jonsson et al., 1977). Benedetti et al. (2004) thinks, that higher pain tolerance found in patients with AD involves reduced autonomic responses what is the cause of diminished emotional processing. The authors suggest that possible anatomic underpinnings of the observed relations may be the degenerative changes within cortical centers responsible for emotions and cooperation with vegetative system, such as orbito-frontal cortex and anterior insulae (Chu et al., 1997).

According to Kunz et al. (2009a) neuropathology associated with dementia affects the pain response system after the threshold of clinical manifestation is reached – before that time it reveals its presence only at the area of the changed reactions of the autonomic system. More and more evidence confirming dysfunctions of sympathetic and parasympathetic system is found (por. Aharon-Peretz et al., 1992; Algotsson et al., 1995; Allan et al., 2007). According to the findings of Kunz and her team (2009b) changes appear before the dementia comes out, already at the stage of mild cognitive impairment (MCI). They found that patients with this diagnosis showed clear reduction of the autonomic system responses to painful stimuli. The remaining components of the pain response system were unaffected, similarly as it was in case of healthy controls. The researchers ascertained, that age and cognitive status are independent predictors of decrease of sympathetic system response for noxious stimuli. Thus, it is suggested that the neuropathological changes associated with MCI affect the pain response system in a way, that is qualitatively different from the physiological changes related to age and aging.

It should be noted, however, that decrease of response concerns only acute pain, in case of chronic pain something opposite may happen. Achterberg et al. (2007) states, that these factors in patients with dementia and suffering from disorder causing chronic pain increase probability of its occurrence. According to Bruehl and Chung (2004), it is a result of reduced activity of the efferent pain inhibition mechanisms caused by recurrent experiencing of it what bears fruit in the form of blood tension increase. Furthermore, as it is indicated by numerous research reports, the vascular risk factors such as hypertension or diabetes are strongly associated with the white matter lesions of subcortical regions (Lazarus et al., 2005; Pugh and Lipsitz, 2002; Van Dijk et al., 2004).

According to the definition, pain experience can be understood as a complex of many response components covering the cognitive and physiological aspect. Quite a popular approach is the assessment of behavior of these components in response to a painful stimulus. Relations between a subjective estimation of experienced pain, facial expression, reflexes and autonomic responses (heart rate) in a situation of experiencing pain by an

individual with dementia are observed. The cognitive estimation of the pain experience by patients with Alzheimer's disease was talked over earlier. Interesting relations occur also with reference to the remaining aspects. Many authors find the increase of facial expression of individuals with dementia in response to unpleasant stimuli (Kunz et al., 2004, 2007, 2008, 2009b; Lautenbachter et al., 2007, Hadjistavropoulos et al., 2000; Porter et al., 1996). What is interesting, such intensity concerns only the pain response, it is not accompanied by general increase of facial expression. Kunz et al. (2007, 2009) is of the opinion, that it results from deficiency of an ability to control cognitive impulses by learned responses of emotions display in social situations in individuals with Alzheimer's disease. Another interpretation assumes, that it is an effect of decline of pain anticipation and situation evaluation in patients of this group (Porter et al., 1996; Benedetti et al., 2004). In the usually employed experimental set patients are provided a series of stimuli, e.g. electrical shocks. Healthy individuals adapt to the situation and in the course of time they start to predict the pain experience what bears fruit in the form of bigger control of facial expression. Patients with dementia cannot conceptualize the series aspect of the situation due to memory deficits, so every time they are surprised by a pain stimulus as if it occurred for the first time. Results obtained by Hsu et al. (2008) are in agreement with this line of reasoning. They investigated oro-facial pain responses during dentist procedures and concluded that the most useful measure for pain recognition in patients was facial expression. They regarded it especially useful in case of individuals with cognitive impairments because in comparison with healthy individuals they displayed less facial responses in anticipation of a pain stimulus, what gives evidence of lack of repeated pain occurrence expectation. What is interesting, in the past it was found that individuals with dementia show smaller emotional expressiveness due to decreased ability to feel emotions as a consequence of separation of self in these patients (Tappen i Williams, 2008).

Kunz et al. (2009a) states that dementia affects various pain components differently. Patients from the investigated group show an increased number of motor reflexes in response to pain (what in connection with increased facial expressiveness would suggest pain processing intensification) and decreased magnitude of autonomic reactions (what suggests reduced pain processing). Probably in the first case we have to do with an artifact because there are research results available that give evidence on dissociation between motor activity and pain sensations (Gracely, 2005, za: Kunz, 2009).

Pain, especially chronic pain, has a destructive influence on an older person functioning, especially the one with dementia. Being in pain leads to occurrence of cognitive (e.g. concentration difficulties) or behavioral symptoms (e.g. apathy), which, if not treated, additionally overlap on existing cognitive deficits (Cook et al., 1999). Fronidini et al. (2007) emphasize neuropsychological aspects of pain experiencing by the elderly – it intensifies short and delayed memory deficits, restricts mental flexibility and may be conducive to language impairments occurrence. In dementia pain manifestation may assume a subtle form (Husebo et al., 2009). According to Weiner et al., (1999) in case of individuals with explicit cognitive impairments such as in advanced Alzheimer's disease it comes to regression to infantile ways of self-expression because their pain, as a result of an inability to cognitively conceptualize it, loses its context. Such patients may show inadequate reactions – cry in response to a weak stimulus such as colonic distention associated with constipation (Weiner et al., 1999). Often, especially in severe dementia, it comes to development of the Behavioral and Psychological Symptoms of Dementia (BPSD; (Zanino et al., 2004; Hersch &

Falzgraf, 2007; Cipher et al., 2006; Onishi et al., 2005). Duggelby & Lander (1994) and also Lynch et al. (1998) suggest that under-treated pain may be an independent factor of delirium development. According to results obtained by the mentioned authors, uncontrolled pain, not taking opioid analgesics is a predictive factor of delirium development in the post-surgery phase.

As it was mentioned before, patients with severe dementia cannot directly communicate their pain experience due to developing deficits of communication skills. As Chibnall et al. (2005) claims pain in patients with moderate and severe dementia weakens activity and restricts engagement in interactions with environment. It may also – being a factor of behavior inhibition – be conducive to intensification of depressive symptoms, including psychomotor slowness, anergy and withdrawal. Patients, instead of complaining signal, often pain in a more subtle way, through nonverbal expression (Shega et al., 2004; Feldt, 2000) and symptoms of depression – worsening of quality of sleep, appetite decrease, withdrawal from activities of daily life (Cohen-Mansfield et al., 1990; Megni et al. 1993; Dworkin et al., 1990; Parmelee et al., 1991) or agitation (Buffum et al., 2000). In the elderly, there is a strong relationship between sensed pain and depression, stronger than in the young adults (Turk, Okifuji, Scharff, 1995). Magni et al. (1996) points to relationship between depression and pain in cognitively intact individuals – they do not find such in case of patients with dementia.

At this point, it is worth discussing an issue of agitation. Batels et al. (2003) defines it as a descriptive term employed for unspecific verbal and physical behaviors which are often met in nursery home residents with dementia. These behaviors include: wandering, motor anxiety, inadequate gestures and verbal outbursts. Prevalence rates of agitation are between 10% and 90% with an average frequency of 44,5% of nursery homes residents. Cohen-Mansfield (1989) distinguishes three subtypes of the agitation: physical aggressive, verbal and physical non-aggressive. Among them the verbal agitation is the most strongly related to pain experiencing. The physical non-aggressive behaviors are associated with better general health and smaller intensification of experienced pain (Villanueva et al., 2003).

There are doubts whether the agitation is a response to pain, especially among supporters of the view suggesting smaller pain feeling by patients with dementia. They point to a fact that intensification of agitated behaviors increases with dementia progression (Cohen-Mansfield et al., 1990), and the agitation remains despite psychotropic medication dosage (Daniel, 2000; Ballard & Burns, 2001). Manfredi et al. (2003b) proved, however, that long-term low-dose opioids treatment decreases frequency of agitation manifestations, especially in patients with dementia at the age of 85 and older.

Kovach et al. (1999) in his investigation on patients with late-stage dementia proved, that among the most often found behaviors, being a response to discomfort, are: distinct gesticulation, sad face expression, fidgeting, persevering verbalisations and verbal outbursts. Other behaviors described in the literature include (Parmalee et al., 1993; Hurley et al., 1992; Buffum et al., 2004, Manfredi et al., 2003b):

- increased agitation, repetitive movements,
- muscle tension,
- increased heart rate, blood tension and sweating,
- breathing aloud,
- facial grimace,
- aggressive behaviors

Kiely et al. (2000), among factors responsible for patients wandering, mentions: cognitive impairments (the deeper deficit, the higher risk) and experienced discomfort.
It is worth mentioning the relation between dementia intensity and behavior disorders, being a response to experienced chronic pain. Cipher et al. (2006), in his research, states that there is an explicit positive relationship between dementia severity and abnormal behaviors. Inappropriate behaviors caused by pain are more often found in patients with the severe stage than in the mild and the moderate ones. Furthermore, the behavior revealed by these individuals is more dysfunctional in comparison with the both remaining groups. Interestingly, detailed analysis proved, that a pain level does not directly affect a patient's everyday functioning. Instead it makes him/her depressed and is a cause of behavior disorders, which are a secondary source of decrease of functioning efficiency. Referring to the distinction made at the beginning of the present work, it can be said that patients with severe dementia in response to acute pain show more frequent and prolonged impulsive and aggressive behaviors that are characterized with bigger intensity than the patients with mild or moderate dementia do. On the other hand patients with severe dementia in response to chronic pain showed bigger intensity of aggressive behaviors, agitation, compulsory repetitive behaviors, delusionally motivated behaviors, wandering and inappropriate social behaviors. In case of patients with mild dementia more frequent unrealistic demands and dysfunctional behaviors have been noted.
At present, at least a dozen or so methods of assessment of pain experienced by patients is available (e.g. PASCLAC, PAINE, PAINAD, MOBID, DOLOPUS etc.). We can divide them into observational scales, basing on others' perceptions concerning a patient, and methods basing on a patient's self-report. Herr et al. (2006; Horgas et al., 2009) made a review of the fourteen scales and stated that these tools were still in an early stage of development, and required more precise psychometric elaboration before they would be able to be recommended to wider clinical employment. Similar conclusions are made by Cook et al. (1999). Most of the pain assessment tools originated on the basis of work with patients with tumour diseases, who were cognitively intact and could report their feelings and sensations (Morrison et al., 1998). Hadjistavropoulos & Craig (2002) claim, that the behavioral scales, including observational ones, measure a more automatic aspect of pain experience, whereas the methods basing on self-report engage higher cognitive centers in a greater degree. With regard to this fact, the methods of the second group may in a greater degree succumb an influence of cognitive, affective and socio-cultural factors. Unfortunately, there is no "golden standard" for the observational pain scales in dementia (Schuler et al., 2007). Then, are there no tools applicable for individuals with dementia? Fortunately, numerous research results indicate, that most of the patients from this group is able to use at least one of the available methods of experienced pain assessment (Cook et al., 1999; Cohen-Mansfield & Lipson, 2008; Zwakhalen et al., 2006; Snow et al., 2004; Scherder & Bouma, 2000). In Ferrel's et al. review (1995) the percentage of patients with dementia able to reliably use the scales, being the topic of the article, oscillated between 35% and 79%. It should be kept in mind, that a scale which is easy and simple from the point of view of a cognitively intact individual may be a very difficult for a patient with dementia. The best example of such a situation is the 100mm analogue scale ("pain thermometer"; Leong et al., 2006). Filling it is apparently easy – a subject is to mark with a cross or a point on a colorful stripe with two poles (respectively: "No pain" and "The worst possible pain") in order to assess intensity of experienced pain. However, this simple task requires an ability to interpret an abstract

thought into a line, recall past states and an ability to manipulate a pencil. Because of this reason only 35% of patients with dementia can use it properly (Ferrell et al., 1995).
Generally, as it is claimed by Mozley et al. (1999), patients with dementia are not eligible for direct questioning about presently experienced pain (in a shape of a talk or employing the measurement scales) when in MMSE:

- they cannot answer correctly at least two of ten questions in the orientation dimension,
- they can answer less than three of eight items in the language functioning dimension and less than two of five in the attention dimension.

Scores on items related to memorizing and visual-constructional abilities did not affect a patient's ability to participate in the examination comprehensively.
The most popular method of pain assessment in nursery homes is basing on perceptions of caregivers – nurses, physicians or relatives. Pain assessment through observation is based on three assumptions (Villanueva et al., 2003):

1. Features of facial expression, posture, movements patterns may indicate presence of pain.
2. Pain can disrupt activities of daily life such as clothing or eating.
3. Caregivers can reliably observe and assess such a behavior.

Generally, with reference to physicians, it can be said that they diagnose pain reliably in patients with mild and moderate cognitive impairments, however their skills of this domain are questionable when considered with regard to patients with severe dementia (Cohen-Mansfield & Lipson, 2002). Sengstaken i King (1993) quote interesting research results – namely, they claim, that in 22% cases, pain complaints of a properly communicating patient were not noted down in a disease history. Moreover, in case of non-communicative patients, only in 17% of them, pain was noted down, what is a flagrant omission in comparison with 43% of communicative residents. Results of Snow's et al. research (2009) support a necessity of noting the information coming from a patient by a medical staff. This author found, that individuals with dementia confirming pain experiencing are at higher risk of negative psychosocial states development.
Numerous investigations on mutual relationships between caregivers' and patients' observations of experienced pain were conducted. Boyer et al. (2004) states, that, paradoxically, caregivers who are not family members present bigger convergence with a patient's opinions than his/her relatives. Similar conclusions are found in the work by Kivak et al. (1994) and Coen et al. (2002) who claim, that family members overestimate patient's functioning disorders, his/her tendency to withdraw, sleep disorders, reactivity and energy level decrease. The authors explain this tendency with a fact that these areas and disorders related to them are a source of a burden for a patient's family. As a confirmation of this way of thinking, the following finding may serve: the biggest discrepancies were between patients' and their relatives' reports, when the relative was a spouse or someone who had very frequent contacts with him/her.
At the same time, there are research results available which opt for an opposite standpoint. At least in case of employment of some of the methods such as MOBID an observer should know a patient well because then he/she obtains more valid scoring (Husebo et al., 2009). Cohen-Mansfield (2002) investigating reliability of relatives' remarks on pain experienced by patients with dementia living in nursery homes found, that their opinions were useful only when they often visited the patient. The author shows, however, the tendencies toward

biasing opinions about the patient, namely: the closer the relationship, the higher perceived level of pain; the more frequent visits, the bigger relative's inclination to observe pain and to raise its level too high. Shega et al. (2004) investigated congruence of marital diads reports about pain experienced by a patient. The authors say that higher congruence was found when a patient was male, not female. This fact can be explained with higher interpersonal sensitivity in women and associated with it skills in identifying the spouse's internal states. Reports congruence had its limits – it decreased significantly in a situation of the patient agitation occurrence.

In conclusion of the following chapter, we will think over what can be done to prevent experiencing pain by patients with dementia or at least to ease their suffering. Pain and its consequences are factors reducing quality of life (QoL) of patients with dementia. According to the definition of World Health Organization QoL is ''the individuals' perceptions of their position in life in the context of the culture and value system in which they live, and in relationship to their goals, expectations, and standards'' (World Health Organization, 1995, in: Torvik et al., 2010). Whitehouse et al. (1997) considering QoL with reference to elderly with dementia, states that it covers cognitive functioning, activities of daily life, social interactions and psychological well-being. Nagamoto et al. (1997) assuming that QoL is a moral and general feeling of well-being investigated its relations with cognitive status, depression, behavior disorders and activities of daily life. Depression proved to be the only one variable significantly correlating with QoL. The other did not show any relationships. The author suggested, that cognitive status may indirectly affect QoL because it can associate with a tendency to behavior disorders displaying. It is of particular importance, in the context of what was said before in this chapter – pain experienced by patients with dementia is conducive to occurring behavior disorders proportionately to severity of dementia and of deficits of verbal communication skills. Gonzalez-Salvador et al. (2000) in his research proved mutual correlations of the all mentioned above factors with QoL and with each other.

There are many ideas, how to improve quality of life of patients with dementia. Volicer et al. (2007) claims, that staff should provide opportunities for participation in meaningful activities, proper medical care and respond to any behavior disorders. The more versatile conception is presented by Brod et al. (1999). He distinguished five areas related to quality of life of individuals with dementia:

1. self-esteem (self-confidence, self-reliance, satisfaction of oneself, making own decisions, reaching own goals),
2. esthetics (an ability to appreciate beauty, nature and environment),
3. positive affect (humour, feeling of happiness, contentment and hope),
4. absence of negative affect (worries, frustration, depression, anxiety, sadness, loneliness, fear, irritability, nervousness, embarrassment and anger),
5. feeling of belonging (feeling of being loved, liked and useful).

Nursery homes staff and relatives of individuals with dementia endeavoring to ensure the highest possible quality of life should then be guided by directives defined by these five areas. It is good to join Brod's guidelines with Kovach's et al. (1999) detailed proposals aiming at improvement of comfort of patients with dementia. This author recommends undertaking the following steps:

- formalizing assessment practice from the point of view of subtle changes in a patient, which may signal experiencing physical pain or affective discomfort,
- development of nurses' assessment skills

- more frequent employment of analgesics as a component of the assessment process which may include analgesia and dosage increase,
- teaching nursery staff about methods of non-pharmacological intervention which improve patient's comfort,
- improvement of skills of communicating results of a patient's condition assessment and negotiating, with a physician, the means of intervention which increase the patient's comfort.

Apart from the above procedures, it is important to mould pain diagnosis skills. There are various approaches to pain recognition available in the literature – some of them focus on moulding skills of specific professionals or emphasize a role of a whole team cooperation. A Hadjistavropoulos's et al. (2007) proposal is a very good example of such an approach and it is worth a closer look. The author describes settlements of the expert board according to which the diagnosis process includes three stages:

1. The first one includes preliminary diagnosis and monitoring of pain experienced by a patient – to reach this goal it employs the above mentioned observational scales, a patient's self-reports etc. Most of the earlier adduced considerations on pain identification in patients concerned this phase precisely. The main role is played by nursery staff and, possibly, a physician responsible for a patient.
2. The second stage comes out when the first one ends with a conclusion that a patient is experiencing pain. A detailed diagnosis of the patient's physical condition, employed medication and functional status is carried out (subjects of the assessment: a possibility of inflammation, sensory disorders, employed drugs, somatic concerns typical for the age, functional status, pain experienced during physical examination). It is an activity area reserved for geriatricians.
3. The third stage includes the assessment of psychosocial factors potentially affecting laying complaints on experienced pain. The assessment at his stage is a task for a psychologist and consists of: a diagnosis of personality, coping mechanisms, psychological well-being, affective, interpersonal and cognitive processes (general and specific) and possible disabilities caused by the pain (also: general and specific).

The above described process is a complex, long-term undertaking, but helps to avoid pitfalls leading to underestimation of pain experienced by patients with dementia and this is the reason why we definitely recommend it. A patient with dementia, especially at the late stage, is completely dependent on environment's favour, what imposes a moral duty on his/her caregivers to ensure him/her the best possible conditions at the end of his/her life. We hope that we succeeded to show in this work that pain, even if not signaled directly by patients of this group, is a common and often predominant experience of their everyday existence.

References

Achterberg, W.P., Scherder, E., Pot, A.M., Ribbe, M.W., (2007) Cardiovascular risk factors in cognitively impaired nursing home patients: A relationship with pain?, *European Journal of Pain*, Vol. 11, pp: 707–710

Achterberg, W. P., Gambassi, G., Finne-Soveri, H., Liperoti, R., Noro, A., Frijters, D. H. M., Cherubini, A., Dell'Aquila, G., Ribbe, M. W., (2010) Pain in European long-term care facilities: Cross-national study in Finland, Italy and the Netherlands, *Pain*, Vol. 148, pp: 70 – 74

Aharon-Peretz, J., Harel, T., Revach, M., Ben-Haim, S.A., (1992) Increased sympathetic and decreased parasympathetic cardiac innervation in patients with Alzheimer's disease, *Arch Neurol* Vol. 49, pp: 919–922.

Algotsson, A., Viitanen, M., Winblad, B., Solders, G. (1995) Autonomic dysfunction in Alzheimer's disease, *Acta Neurol Scand*, Vol. 91, pp: 14–18

Allan, L.M., Ballard, C.G., Allen, J., Murray, A., Davidson, A.W., McKeith, I.G., Kenny, R.A., (2007) Autonomic dysfunction in dementia, *J Neurol Neurosurg Psychiatry*, Vol. 78, pp: 671–677

Bachino, C., Snow, A.L., Kumik, M. (2001) Principles of pain assessment and treatment in non-communicative demented patients, *Clin Gerontol*, Vol. 23, pp: 97–115

Ballard, H.R., Burns, O.J., (2001) Guidelines for the management of agitation in dementia, *Int J Geriatr Psychiatry,* Vol. 16, No. 7, pp: 714–717

Bartels, S.J., Horn,S.D., Smout, R.J., Dums, A.R., Flaherty, E., Jones, J.K., Monane, M., Taler, G.A., Voss, A.C., (2003) *Am J Geriatr Psychiatry*, Vol. 11, pp: 231 – 238

Benedetti, F., Vighetti, S., Ricco, C., Lagna, E., Bergamasco, B., Pinessi, L., Rainero, I., (1999) Pain threshold and tolerance in Alzheimer's disease, *Pain*, Vol. 80, pp: 377–82

Benedetti, F., Arduino, C., Vighetti, S., Asteggiano, G., Tarenzi, L., Rainero, I., (2004) Pain reactivity in Alzheimer patients with different degrees of cognitive impairment and brain electrical activity deterioration, *Pain*, Vol. 111, pp: 22–29

Benedetti, F., Arduino, C., Costa, S., Vighetti, S., Tarenzi, L., Rainero, I., Asteggiano, G., (2006) Loss of expectation-related mechanisms in Alzheimer's disease makes analgesic therapies less effective, *Pain*, Vol. 121, pp: 131 – 144

Blennow, K., Wallin, A., Hager, O., (1993) Low frequency of post-lumbar puncture headache in demented patients, *Acta Neurol Scand*, 88, pp: 221–223

Boyer, F., Novella, J. L., Morrone, I., Jolly, D., Blanchard, F., (2004) Agreement between dementia patient report and proxy reports using the Nottingham Health Profile, *Int J Geriatr Psychiatry*, Vol. 19, pp: 1026–1034

Brod, M., Stewart, A. L., Sands, L., & Walton, P. (1999) Conceptualization and measurement of quality of life in dementia: The Dementia Quality of Life instrument (DqoL), *The Gerontologist*, Vol. 39, No. 1, pp: 25–35

Bruehl, S., Chung, O.Y., (2004) Interactions between the cardiovascular and pain regulatory systems: an updated review of mechanisms and possible alterations in chronic pain, *Neurosci Biobehav Rev*, Vol. 28, pp: 395–414

Buffum, M.D., Miaskowski, C., Sands, L., Brod, M., (2001) A pilot study of the relationship between discomfort and agitation in patients with dementia, *Geriatr Nurs*, Vol. 22, pp: 80–88

Chibnall, J. T., Tait, R.C., Harman, B., Luebbert, R. A., (2005) Effect of Acetaminophen on Behavior, Well-Being, and Psychotropic Medication Use in Nursing Home Residents with Moderate-to-Severe Dementia, *J Am Geriatr Soc*, Vol. 53, pp: 1921–1929

Chu, C.C., Tranel, D., Damasio, A.R., Van Hoesen, G.W., (1997) The autonomic-related cortex: pathology in Alzheimer's disease, *Cereb Cortex*, Vol. 7 pp: 86–95.

Cipher, D. J., Clifford, P. A., (2004) Dementia, pain, depression, behavioral disturbances, and ADLs: toward a comprehensive conceptualization of quality of life in long-term care, *Int J Geriatr Psychiatry*, Vol. 19, pp: 741–748

Cipher, D. J., Clifford, A., Roper, K. D., (2006) Behavioral Manifestations of Pain in the Demented Elderly, *J Am Med Dir Assoc*, Vol. 7, pp: 355–365

Coen, R.F., O'Boyle, C.A., Coakley, D., Lawlor, B.A., (2002) Individual quality of life factors distinguishing low-burden and high-burden caregivers of dementia patients, *Dement Geriatr Cogn Disord*, Vol. 13, No. 3, pp: 164–170

Cohen-Mansfield, J., (1989) Agitation in the elderly, *Adv Psychosom Med*, Vol. 19, pp: 101–113

Cohen-Mansfield, J., Billig, N., Lipson, S., Rosenthal, A.S., Pawlson, L.G., (1990) Medical correlates of agitation in nursing home residents, *Gerontology*, Vol. 36, pp: 150–158

Cohen-Mansfield, J., (2002) Relatives' Assessment of Pain in Cognitively Impaired Nursing Home Residents, *J Pain Symptom Manage*, 24, pp: 562–571

Cohen-Mansfield, J., Lipson, S., (2002), Pain in Cognitively Impaired Nursing Home Residents: How Well Are Physicians Diagnosing It?, *J Am Geriatr Soc*, Vol. 50, pp: 1039–1044

Cohen-Mansfield, J., Lipson, S., (2008) The utility of pain assessment for analgesic use in persons with dementia, *Pain*, Vol. 134, pp: 16–23

Cole, L.J., Farrell, M.J., Duff, E.P., (2006) Pain sensitivity and fMRI pain-related brain activity in Alzheimer's disease, *Brain*, Vol. 129, pp: 2957–2965

Cook, A. K. R., Niven, C. A., Downs, M. G., (1999) Assessing the pain of people with cognitive impairement, *Int. J. Geriat. Psychiatry*, Vol. 14, pp; 421-425

Cornali, C., Franzoni, S., Gatti, S., Trabucchi, M., (2006) Diagnosis of Chronic Pain Caused by Osteoarthritis and Prescription of Analgesics in Patients With Cognitive Impairment, *J Am Med Dir Assoc*, Vol. 7, pp: 1–5

Daniel, D.G., (2000) Antipsychotic treatment of psychosis and agitation in the elderly, *J Clin Psychiatry*, Vol. 61, Suppl. 14, pp: 49–52

Duggleby, W., Lander, J., (1994) Cognitive status and postoperative pain: older adults, *J Pain Symptom Manage*, Vol. 9, pp: 19–27

Dworkin, S.F., Von Korff, M., LeResche, L., (1990) Multiple pains and psychiatric disturbance: an epidemiologic investigation, *Arch Gen Psychiatry*, Vol. 47, pp: 239–244

Evers, M. M., Meier, D. E., Morrison, R. S., (2002) Assessing Differences in Care Needs and Service Utilization in Geriatric Palliative Care Patients, *J Pain Symptom Manage*, pp: 424–432

Feldt, K., (2000) Checklist of nonverbal pain indicators, *Pain Manage Nurs*, Vol. 1, pp: 13–21

Ferrell, B.A., Ferrell, B.R., Osterweil, D., (1990) Pain in the nursing home, *J Amer Geriatr Soc,* Vol. 38, pp: 409–414

Ferrell, B.A., Ferrell, B.R., Rivera, L., (1995) Pain in cognitively impaired nursing home patients, *J Pain Symptom Manage,* Vol. 10, pp: 591–598

Fine, P. G., (2009) Chronic Pain Management in Older Adults: Special Considerations, *J Pain Symptom Manage*, 38, pp: 4-14

Fisher, S.E., Burgio, L.D., Thorn, B.E., Allen-Burge, R., Gerstle, J., Roth, D.L., (2002) Pain assessment and management in cognitively impaired nursing home residents: association of certified nursing assistant pain report, minimum data set pain report, and analgesic medication use, *J Am Geriatr Soc*, Vol. 50, pp: 152–156

Fries, B.E., Simon, S.E., Morris, J.N. (2001) Pain in U.S. nursing homes. Validating a pain scale for the Minimum Data Set, *Gerontologist*, Vol. 2, pp: 173–179.

Frondini, C., Lanfranchi, G., Minardi, M., Cucinota, D., (2007) Affective, Behavior and Cognitive Disorders in the Elderly with Chronic Musculoskeletal Pain: the Impact on Aging Population, *Arch. Gerontol. Geriatr. Suppl*., Vol. 1, pp: 167 – 171

Gibson, S.J., Helme, R.D., (2001) Age-related differences in pain perception and report, *Clin Geriatr Med,* Vol. 17, pp: 433–456

Gibson, S.J., Voukelatos, X., Ames, D., Flicker, L., Helme, R.D. (2001) An examination of pain perception and cerebral event-related potentials following carbon dioxide laser stimulation in patients with Alzheimer's disease and age-matched control volunteers, *Pain Res Manag,* Vol. 6, pp: 126–32

Gonzalez-Salvador, T., Lyketsos, C.G., Baker, A., (2000) Quality of life in dementia patients in long-term care, *Int J Geriatr Psychiatry*, Vol. 15, pp: 181–189

Gruneir, A., Miller, S. C., Lapane, K. L., Kinzbrunner, B., (2006) Hospice Care in the Nursing Home: Changes in Visit Volume from Enrollment to Discharge Among Longer-Stay Residents, *J Pain Symptom Manage*, 32, pp: 478-487

Hadjistavropoulos, T., Herr, K., Turk, D.C., (2007) An interdisciplinary expert consensus statement on assessment of pain in older persons, *Clin J Pain*, Vol. 23, pp:1-43

Herr, K., Bjoro, K., Decker, S., (2006) Tools for Assessment of Pain in Nonverbal Older Adults with Dementia: A State-of-the-Science Review, *Journal of Pain and Symptom Management*, Vol. 31, No. 2, pp. 170 – 192

Hersch, E. C., Falzgraf, S., (2007) Management of the behavioral and psychological symptoms of dementia, *Clinical Interventions in Aging*, 2(4), pp. 611–621

Horgas, A. L., Elliott, A. F., Marsiske, M., (2009) Pain Assessment in Persons with Dementia: Relationship Between Self-Report and Behavioral Observation, *JAGS*, Vol. 57, No. 1, pp: 126 – 132

Hadjistavropoulos, T., Craig, K.D., (2002) A theoretical framework for understanding self-report and observational measures for pain: a communications model, *Behav Res Ther*, Vol. 40, pp: 551–570

Hsu, K.T., Shuman, S.K., Hamamoto, D.K., Hodges, J.S., Feldt, K.S., (2007) The application of facial expressions to the assessment of orofacial pain in cognitively impaired older adults, *J Am Dent Assoc, Vol.* 138, pp: 963-969

Hurley, A.C., Volicer, B.J., Hanrahan, P.A., (1992), Assessment of discomfort in advanced Alzheimer patients, *Res Nurs Health*, Vol. 15, pp: 369–377

Husebo, B. S., Strand, L. I., Moe-Nilssen, R., Husebo, S. B., Aarsland, D., Ljunggren, A. E., (2008) Who Suffers Most? Dementia and Pain in Nursing Home Patients: A Cross-sectional Study, *J Am Med Dir Assoc*, Vol. 9, pp: 427–433

Husebo, B.S., Strand, L.I., Moe-Nilssen, R., Husebo, S.B., Ljunggren, A.E., (2009) Pain behaviour and pain intensity in older persons with severe dementia: reliability of the MOBID Pain Scale by video uptake, *Scand J Caring Sci*, Vol. 23, pp: 180–189

Jonsson, C.O., Malhammar, G., Waldton, S., (1977) Reflex elicitation thresholds in senile dementia. *Acta Psychiatr Scand*, Vol. 55, pp: 81–96

Kamel, H. K., Phlavan, M., Malekgoudarzi, B., Gogel, P., Morley, J. E., (2001) Utilizing Pain Assessment Scales Increases the Frequency of Diagnosing Pain Among Elderly Nursing Home Residents, *J Pain Symptom Manage*, 21, pp: 450–455

Kiely, D., Morris, J. N., Aglase, D. L., (2000) Resident characteristics associated with wandering in nursing homes, *Int J Geriatr Psychiatry*, vol. 15, pp: 1013 – 1020

Kiyak, H.A., Teri, L., Borson, S., (1994) Physical and functional health assessment in normal aging and in Alzheimer's disease: selfreport vs family reports, *Gerontologist*, Vol. 34, pp: 324–330

Kovach, Ch. R., Weissman, D. E., Griffie, J., Matson, S., Muchka, S., (1999) Assessment and Treatment of Discomfort for People with Late-Stage Dementia, *J Pain Symptom Manage*, 18, pp: 412–419

Krulewitch, H., London, M.R., Skakel, V.J., (2000) Assessment of pain in cognitively impaired older adults: a comparison of pain assessment tools and their use by nonprofessional caregivers, *J Amer Geriatr Soc,* Vol. 48, pp: 1607–1611

Kunz, M., Mylius, V., Schepelmann, K., Lautenbacher, S., (2004) On the Relationship Between Self-Report and Facial Expression of Pain, *The Journal of Pain*, Vol 5, No 7 (September), pp. 368-376

Kunz, M., Scharmann, S., Hemmeter, U., Schepelmann, K., Lautenbacher, S., (2007) The facial expression of pain in patients with dementia, *Pain*, 133, pp. 221–228

Kunz, M., Mylius, V., Schepelmann, K., Lautenbacher, S., (2008) Impact of age on the facial expression of pain, *Journal of Psychosomatic Research*, 64, pp. 311–318

Kunz, M., Mylius, S., Schepelman, K, Lautenbachter, S., (2009a) Effects of Age and Mild Cognitive Impairment on the Pain Response System, *Gerontology*, Vol. 55, pp: 674 – 682

Kunz, M., Mylius, S., Scharmann, M., Schepelman, K, Lautenbachter, S., (2009b) Influence of dementia on multiple components of pain, *European Journal of Pain*, Vol. 13, pp: 317–325

Kwentus, J.A., Harkins, S.W., Lignon, N., (1985) Current concept of geriatric pain and its treatment, *Geriatrics*, Vol. 40, pp: 48–57

Lazarus, R., Prettyman, R., Cherryman, G., (2005) White matter lesions on magnetic resonance imaging and their relationship with vascular risk factors in memory clinic attenders, *Int J Psychiatry*, Vol. 20, No. 3, pp: 274–279

Leone, A. F., Standoli. F., Hirth, V., (2009) Implementing a Pain Management Program in a Long-Term Care Facility Using a Quality Improvement Approach, *J Am Med Dir Assoc*, Vol. 10 pp: 67–73

Leong, I., Chong, M. S., Gibson, S. J., (2006) The use of a self-reported pain measure, a nurse-reported pain measure and the PAINAD in nursing home residents with moderate and severe dementia: a validation study, *Age and Ageing*, Vol. 35, pp: 252 – 256

Leong, I.Y., Nuo, T.H., (2007) Prevalence of pain in nursing home residents with different cognitive and communicative abilities, *Clin J Pain*, Vol. 23, pp: 119–127

Lynch, E.P., Lazor, M.A., Gellis, J.E., Orav, J., Goldman, L., Marcantonio, E.R., (1998) The impact of postoperative pain on the development of postoperative delirium, *Anesth Analg*, Vol. 86, pp: 781–785

Magni, E., Frisoni, G. B., Rozzini, R., De Leo, D., Trabucchi, M., (1996) Depression and Somatic Symptoms in the Elderly: The Role of Cognitive Function, *Int. J. Geriat. Psychiatry*, Vol. 11, pp; 517 – 522

Manfredi, P. L., Breuer, B., Meier, D. E., Libow, L., (2003a) Pain Assessment in Elderly Patients with Severe Dementia, *J Pain Symptom Manage*, 25, pp: 48–52

Manfredi, P. L., Breuer, B., Wallenstein, S., Stegmann, M., Bottomley, G., Libow, L., (2003b) Opioid treatment for agitation in patients with advanced dementia, *Int J Geriatr Psychiatry*, Vol. 18, pp: 700–705

Mantyselka, P., Hartikainen, S., Louhivuori-Laako, K., Sulkava, R., (2004) Effects of dementia on perceived daily pain in home-dwelling elderly people: a population-based study, *Age and Ageing*, Vol. 33, pp: 496–499

Marzinski, L.R., (1991) The tragedy of dementia: clinically assessing pain in the confused, nonverbal elderly, *J Gerontol Nurs*, Vol. 17, pp: 25-28

Megni, G., Mchetti, M., Moreschi, C., (1993) Chronic musculoskeletal pain and depressive symptoms in the National Health and Nutrition Examination: I. Epidemiologic follow-up study, *Pain*, Vol. 53, pp: 163–168

Melding, P.S., (1991) Is there such a thing as geriatric pain?, *Pain*, Vol. 46, pp: 119–121

Melzack R, Wall, P.D., (1965) Pain mechanisms: a new theory. *Science,* Vol. 150, pp: 971–979

Merlino, I., Sabattoli, F., Riello, R., Geroldi, C., Zanetti, O., Frisoni, G. B., (2002) Physical complaints do not decrease linearly with increasing cognitive impairment, *Int J Geriatr Psychiatry*, Vol. 17, pp: 1073–1075

Mersky, H., (1986) Classification of chronic pain: Description of chronic pain syndromes and definition of pain terms, *Pain,* S1(3)

Miaskowski, C., (2000) The impact of age on a patient's perception of pain and ways it can be managed, *Pain Management Nursing*, Vol. 1, No. 3, pp: 2–7

Morrison, R. S., Ahronheim, J. C., Morrison, R., Darling, E., Baskin, S. A., Morris, J., Choi, Ch., Meier, D. E., (1998) Pain and Discomfort Associated with Common Hospital Procedures and Experiences, *J Pain Symptom Manage*, 15, No. 2, pp: 91 – 101

Morrison, R. S., , Siu, A. L., (2000) A Comparison of Pain and Its Treatment in Advanced Dementia and Cognitively Intact Patients with Hip Fracture, *J Pain Symptom Manage*, 19, pp: 240–248

Mozley, C.G., Huxley, P., Sutcliffe, C., (1999) 'Not knowing where I am doesn't mean I don't know what I like': cognitive impairment and quality of life responses in elderly people, *Int J Geriat Psychiatry*, Vol. 14, pp: 776–783

Nagamoto, I., Kita, K., Takigawa, M., Nomaguchi, M., Sameshima, K., (1997) A study of the quality of life in elderly people using psychological testing, *Int J Geriatr Psychiatry*, Vol. 12, pp: 599–608

Nygaard, H. A., Jarland, M., (2005) Are nursing home patients with dementia diagnosis at increased risk for inadequate pain treatment?, *Int J Geriatr Psychiatry*, Vol. 20, pp: 730–737

Onishi, J., Suzuki, Y., Umegaki, H., Nakamura, A., Endo, H., Iguchi, A., (2005) Influence of behavioral and psychological symptoms of dementia (BPSD) and environment of care on caregivers' burden, *Archives of Gerontology and Geriatrics*, Vol. 41, pp: 159–168

Parke, B., (1998) Realizing the presence of pain in cognitively impaired older adults: gerontological nurses' ways of knowing, *J Gerontol Nurs*, Vol. 24, No. 6, pp: 21–28

Parmelee, P.A., Katz, I.R., Lawton, M.P., (1991) The relation of pain to depression among institutionalized aged, *J Gerontol*, Vol. 46, pp: 15–21

Parmelee, P.A., Smith, B., Katz, I.R., (1993) Pain complaints and cognitive status among elderly institution residents, *J Amer Geriatr Soc*, Vol. 41, pp: 517–522.

Parmelee, P.A., (1996) Pain in cognitively impaired older persons, *Clin Geriatr Med*, Vol. 12, pp: 473–479

Pautex, S., Michon, A., Guedira, M., Emond, H., Le Lous, P., Samaras, D., Michel, J. P., Herrmann,F.,Giannakopoulos, P., Gold, G., (2006) Pain in Severe Dementia: Self-Assessment or Observational Scales?, *J Am Geriatr Soc*, Vol. 54, pp: 1040–1045

Porter, F.L., Malhotra, K.M., Wolf, C.M., Morris, J.C., Miller, J.P., Smith, M.C., (1996) Dementia and response to pain in the elderly, *Pain*, Vol. 68, pp: 413–21

Proctor, W.R., Hirdes, J.P., (2001) Pain and cognitive status among nursing home residents in Canada, *Pain Res Manage*, Vol. 6, pp: 119–125

Pugh, K.G., Lipsitz, L.A. (2002) The microvascular frontal-subcortical syndrome of aging. *Neurobiol Aging*, Vol. 23, pp: 421–31

Rainero, I., Vighetti, S., Bergamasco, B., Pinessi, L., Benedetti, F., (2000) Autonomic responses and pain perception in Alzheimer's disease, *Eur J Pain*, Vol. 4, pp: 267–274

Reynolds, K. S., Hanson, L. C., DeVellis, R. F., Henderson, M., Steinhauser, K. E., (2008) Disparities in Pain

Management Between Cognitively Intact and Cognitively Impaired Nursing Home Residents, *J Pain Symptom Manage*, 35, pp: 388-396

Sawyer, P., Lillis, P., Bodner, E. V., Allman, R. M., (2007) Substantial Daily Pain Among Nursing Home Residents, *J Am Med Dir Assoc,* Vol. 8, pp: 158–165

Scherder, E., Bouma, A., Borkent, M., Rahman, O., (1999) Alzheimer patients report less pain intensity and pain affect than non-demented elderly, *Psychiatry*, Vol. 62, pp: 265–72

Scherder, E., Bouma, A., (2000) Acute versus chronic pain experience in Alzheimer's disease: A new questionnaire, *Dementia and Geriatric Cognitive Disorders;* Jan/Feb, Vol. 11, pp: 11 – 16

Scherder, E., Bouma, A., Slaets, J., Ooms, M., Ribbe, M., Blok, A., Sergeant, J., (2001) Repeated Pain Assessment in Alzheimer's Disease, *Dement. Geriatr. Cogn. Disord.*, Vol. 12, pp: 400 – 407

Scherder, E.J., Sergeant, J.A., Swaab, D.F., Huffman, J.C., Kunik, M.E., (2003) Pain processing in dementia and its relation to neuropathology, *Lancet Neurol*, pp: 677-686

Scherder, E.J., Slaets, J., Deijen, J.B., (2003) Pain assessment in patients with possible vascular dementia, *Psychiatry*, Vol. 66, pp: 133-145

Schuler, M. S., Becker, S., Kaspar, R., Nikolaus, T., Kruse, A., Basler, H. D., (2007) Psychometric Properties of the German "Pain Assessment in Advanced Dementia Scale" (PAINAD-G) in Nursing Home Residents, *J Am Med Dir Assoc*, Vol. 8, pp: 388–395

Sengstaken, E.A., King, S.A., (1993) The problems of pain and its detection among geriatric nursing home residents, *J Am Geriatr Soc*, Vol. 41, pp: 541–558

Shega, J. W., Hougham, G.W., Stocking, C. B., Cox-Hayley, D., Sachs, G. A., (2004) Pain in Community-Dwelling Persons with Dementia: Frequency, Intensity, and Congruence Between Patient and Caregiver Report, *J Pain Symptom Manage*, 28, pp: 585–592

Shega. J. W., Hougham, G. W., Stocking, C. B., Cox-Hayley, D., Sachs, G. A., (2006) Management of Noncancer Pain in Community-Dwelling Persons with Dementia, *J Am Geriatr Soc*, Vol. 54, pp: 1892–1897

Snow, A. L., Weber, J. B., O'Malley, K. J., Cody, M., Beck, C., Bruera, E., Ashton, C., Kunik, M. E., (2004) NOPPAIN: A Nursing Assistant-Administered Pain Assessment Instrument for Use in Dementia, *Dement. Geriatr. Cogn. Disord.*, Vol. 17, pp: 240 – 246

Snow, A.L., Chandler, J.F., Kunik, M.E., Davila, J.A., Balasubramanyam, V., Stelle, A.B., Morgan, R.O., (2009) Self-
Reported Pain in Persons With Dementia Predicts Subsequent Decreased Psychosocial Functioning, *Am J Geriatr Psychiatry*, Vol. 17, No.10, pp: 873 – 880
Stein, W.M., Ferrell, B.A., (1996) Pain in the nursing home, *Clin Geriat Med*, Vol. 12, pp: 601–613
Tappen, R. M., Williams, Ch. L., (2008) Development and Testing of the Alzheimer's Disease and Related Dementias Mood Scale, *Nurs Res*., 57(6): 426–435
Teno, J.M., Weitzen, S., Wetle, T. (2001) Persistent pain in nursing home residents, *JAMA,* Vol. 285, pp: 2081
Torvik, K., Kaasa, S., Kirkevold, O, Rustoen, T., (2010) Pain and Quality of Life Among Residents of Norwegian Nursing Homes, *Pain Management Nursing*, Vol. 11, No. 1, pp: 35 – 44
Turk, D., Okifuji, A., Scharff, L., (1995) Chronic pain and depression: Role of perceived impact and perceived control in different age cohorts, *Pain*, Vol. 61, pp: 93–101
Van Dijk, E.J., Breteler, M.M.B., Schmidt, R., Berker, K., Nilsson, L.-G., Oudkerk, M., (2004) For the CASCADE Consortium. The association between blood pressure, hypertension, and cerebral white matter lesions: cardiovascular determinants of dementia study, *Hypertension*, Vol. 44, pp: 625–30
Villanueva, M. R., Smith, T. L., Erickson, J. S., Lee, A. C., Singer, C. M., (2003) Pain Assessment for the Dementing Elderly (PADE): Reliability and Validity of a New Measure, *J Am Med Dir Assoc*, Vol. 4, pp: 1–8
Volicer, L., (2007) Goals of care in advanced dementia: Quality of life, dignity and comfort, *Journal of Nutrition, Health & Aging*, Vol. 11, No. 6, pp: 481
Weiner, D., Peterson, B., Keefe, F., (1999) Chronic pain-associated behaviors in the nursing home: resident versus caregiver perceptions, *Pain*, Vol. 80, pp: 577–588
Whitehouse, P.J., Orgogozo, J.M., Becker, R.E., (1997) Quality of life assessment in dementia drug development, *Alzheimer Dis Assoc Disord*, Vol. 11, No. 3, pp: 56–60
Zanino, G., Gargiulo, A., Lamenza, F., Marotta, M. G., Barzotti, T., Silvestri, A., Ettorre, E., Marigliano, V., (2004) The Management of Psychogeriatric Patient, *Arch. Gerontol. Geriatr.,* Suppl. 9, pp: 465 – 470
Zwakhalen, S. M. G., Hamers, J. P. H., Berger, M. P. F., (2006) The psychometric quality and clinical usefulness of three pain assessment tools for elderly people with dementia, *Pain*, Vol. 126, pp: 210–220
Zwakhalen, S.M.G., Hamers, J.P.H., Peijnenburg, R.H.A., Berger, M.P.F., , (2007) Nursing staff knowledge and beliefs about pain in elderly nursing home residents with dementia, *Pain Research & Management : The Journal of the Canadian Pain Society;* Autumn, Vol. 12, No. 3, pp: 177 – 184
Zwakhalen, S.M.G., Koopmans, R.T.C.M., Geels, P. J.E.M., Berger, M.P.F., Hamers, J.P.H., (2009), The prevalence of pain in nursing home residents with dementia measured using an observational pain scale, *European Journal of Pain*, Vol. 13, pp: 89–93

4

Treatment of childhood pneumonia in developing countries

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Introduction

Definition of community acquired pneumonia (CAP)

CAP can be defined clinically as the presence of signs and symptoms of pneumonia in a previously healthy child due to an acute infection (of less than 14 days' duration) of the lower respiratory tract (usually occurs below terminal bronchioles) leading to cough or difficult breathing, tachypnoea, or lower chest-wall indrawing, which has been acquired in the community outside hospital (Zar et al., 2005; BTS, 2002). In developed countries this can be verified by the radiological finding of consolidation (BTS, 2002). In resource poor setting of the developing world, a more practical term - acute lower respiratory infection (ALRI) - is preferred, reflecting the difficulties in obtaining a chest radiograph, especially in rural areas (BTS, 2002).

Disease burden and epidemiology of CAP

In the developing world, pneumonia is not only more common than it is in Europe and North America (Riley et al.,1983; Berman & McIntosh, 1985; Selwyn, 1990), but also more severe and is the largest killer disease of children (Bulla & Hitze, 1978; Baqui et al., 1998). The fourth Millennium Development Goal has concentrated efforts on addressing the priority areas for improving child survival worldwide, with an aim of reducing the national child mortality rates by two-thirds by 2015 (UN, 2000). ALRI, particularly pneumonia, are currently the leading and biggest single cause of deaths among under-5 children 1 to 59 months of age in the developing countries (UNICEF & WHO, 2006; Graham et al., 2008), being responsible for at least 19% of the annual 8.8 million deaths in this age-group (Wardlaw et al., 2006). ALRI causes more than 2 million child deaths (one million in children aged 1 to 59 months and additional one million in neonates) worldwide each year, mostly from pneumonia, accounting for 20% of deaths in under-5 children (Bryce et al., 2005; Rudan et al., 2004), and 90-95% of all these deaths occur in the developing countries (Rudan et al., 2008; Murray & Lopez, 1997; Garenne et al., 1992; Mulholland, 1999; Williams et al., 2002; WHO, 1998). In terms of magnitude of the problem, there is an estimated incidence of 151 million new cases of pneumonia each year globally, and 11-20 million (7-13%) are severe enough to require hospitalization in the developing countries (Rudan et al., 2004; Rudan et

al., 2008). Recent estimates also suggest that 1.9 million (95% CI 1.6 to 2.2 million) children died from acute respiratory infection (ARI) throughout the world in 2000 and 70% of them occurred in Africa and Southeast Asia, one dying in every 7 seconds (Mulholland, 1999; Williams et al., 2002). Actually, CAP is a major cause of health care utilization, hospitalization, and death in children in the developing countries (Mulholland, 1999; Williams et al., 2002; WHO, 1998). Therefore, improvement in the case-management strategies of the major causes of child death, such as pneumonia and neonatal illnesses in developing countries, should be a priority in improving the child survival in the developing countries (Walley et al., 2008; Duke & Tamburlini, 2003). ARI is also a major cause of visits to the outpatient and emergency departments as well as admissions to the hospitals. Although bronchiolitis, tracheobronchitis and pneumonia, each accounts for one-third of ALRI cases, pneumonia is responsible for most of the ALRI deaths. In Bangladesh, ALRI account for 25% of deaths among under-5 children and constitute 40% of all infantile deaths (Baqui et al., 1998). In a study conducted at the Dhaka Hospital of ICDDR,B among 401 under-5 children with ALRI, it was observed that the most common manifestation was pneumonia and a respiratory pathogen (both bacterial and viral) was identified in 30% cases and the case fatality rates were 14% in bacterial pneumonia and 3% in viral pneumonia (Rahman et al., 1990). In another study also conducted at the Dhaka Hospital of ICDDR,B among 601 under-5 children with ALRI, it was observed that the most common manifestation was pneumonia (86.5%), and a viral pathogen was detected in 21% cases, and the overall case fatality rate was 6.8%, and that of viral pneumonia was 4.8% (Huq et al., 1990).

Objective

To develop guidelines for the physicians and nurses of the developing countries for the diagnosis and management of CAP in children

Options

- Clinical assessment
- Radiographic assessment
- Laboratory testing
- Empirical antimicrobial therapy

Outcomes

- Increased awareness of the age-related causes of CAP including those children with severe acute malnutrition (SAM), and those with dehydrating diarrhoea
- Improved accuracy of clinical diagnosis of CAP in children
- Better utilization of the available diagnostic testing
- Rational use of empirical antimicrobial therapy
- Decreased morbidity and mortality due to CAP

Benefits, harms, and costs

- Increased awareness of the causes of paediatric pneumonia
- Accurate diagnosis
- Prompt treatment
- Reduced cost associated with unnecessary investigations and complications due to inappropriate treatment

Rationale

As pneumonia is a major cause of morbidity and mortality in children in the developing countries (Williams et al., 2002), early and appropriate treatment of pneumonia can reduce the morbidity and mortality (Sazawal & Black, 2003), which has been the rationale for the development of guidelines for the management of CAP (Zar et al., 2005). The guidelines also aim to provide recommendations for effective therapy and to minimize the development of bacterial resistance through judicious use of antibiotics (Zar et al., 2005). This document aims to provide guidelines for the diagnosis and effective management of children with CAP so as to improve pneumonia-associated morbidity and mortality, thereby improving the case-management strategies of the major cause of child death, such as pneumonia in the developing countries which should be a priority in improving child survival globally (Walley et al., 2008; Duke & Tamburlini, 2003).

Clinical classification and management plan of CAP

Depending on the clinical presentation, pneumonia can be classified as very severe, severe, or non-severe according to the World Health Organization (WHO) (WHO, 1990; WHO, 1984; WHO, 2000; WHO, 1991). The specific treatment guidelines for each of them, and the diagnosis of pneumonia should primarily be based on the visible clinical parameters, including respiratory rate and lower chest-wall indrawing (WHO, 1990; WHO, 1991; Cashat et al., 2005). Pneumonia is usually caused by viruses or bacteria, but the most serious episodes are caused by bacteria. However, in the absence of clear cut demarcation for aetiological diagnosis of pneumonia on the basis of clinical and/or radiological features, empiric antibiotic therapy is needed for all cases of CAP. Hospitalization of children with severe pneumonia is recommended for giving supportive treatment including oropharyngeal or nasopharyngeal suction, oxygen therapy for hypoxaemia, fluid and nutritional management, and close monitoring (WHO, 1990; WHO, 1984; WHO, 2000; WHO, 1991). Therefore, management of severe childhood pneumonia relies on hospital-based treatment, but practical barriers often prevent children in areas with highest rates from receiving hospital care (Ashraf et al., 2008). In the developing countries, there are not enough paediatric beds in hospitals for admission of all severe cases of pneumonia (Ashraf et al. 2008). In addition, hospitalization may not be possible because of the inability of the parents to visit the hospital because of the long distances to travel or financial or other domestic reasons, such as the need to care for siblings at home and the need for the mother to work (Ashraf et al., 2008; Ashraf et al., 2007). It is, therefore, important to provide some form of institutional care for children who cannot be hospitalized, at least until stabilization of their acute condition (Ashraf et al., 2008). Radiological examination and determination of hypoxaemia by pulse oximetry, have been recently considered as the optimal methods for diagnosing pneumonia. But, they are clearly suitable only for use in the institutional settings like the day-care centres or out-patient clinics. Two prospective observational studies have shown that the day-care facility-based, modified primary care management of severe childhood pneumonia (Ashraf et al., 2008) and severe acute malnutrition (SAM) (Ashraf et al., 2007) is successful and cost-effective as an alternative to hospitalization. Provision of broad-spectrum antibiotics and appropriate supportive care during a stay at established day-care centre during their working hours, followed by the continuation of care at home at night, is an effective alternative to hospitalization of children with severe pneumonia without associated co-morbidities such as SAM (Ashraf et al., 2008). The results of this study

indicate that severe childhood pneumonia without SAM can be successfully managed on a day-care basis at established day-care clinics, if adequately trained and motivated staff and the necessary logistic support can be made available (Ashraf et al., 2008). The results of a randomized controlled clinical trial (RCT) have shown that in a select group of under-5 children with severe pneumonia, without associated co-morbidities such as SAM, can be safely and effectively managed on a day-care basis as effectively as the hospital set-up management, except those children with hypoxaemia requiring prolonged oxygen therapy for more than six hours, and that day-care based treatment option is less expensive than hospital-care (Ashraf et al., 2010). The results also indicate that severe pneumonia without hypoxaemia can be successfully managed on a day-care basis at a day-care clinic, however, identification of those severely pneumonic children having hypoxaemia requiring prolonged oxygen therapy for more than six hours are necessary, as they are at increased risk of death and therefore need to be hospitalized for support and care for a longer period of time (Ashraf et al., 2010). These results would have great impact in the treatment and care of childhood pneumonia, particularly in resource-poor countries where hospital beds are scarce. It can be easily replicated in most urban and rural out-patient clinics and day-care centres, provided that proper training and motivation of the staff as well as provision of logistic support are guaranteed. The additionally needed funds are well invested facing the lower costs of the day-care treatment model compared to those of hospital-care (US$ 114 vs. 178) (Ashraf et al., 2010). However, policy and programme changes would be necessary to add such components to the out-patient clinics and day-care centres, and this would require additional human and financial resources, which is not an easy task. Therefore, this would be important in selecting the intervention for wider implementation in national programmes. The results of our RCT identified a way to more efficiently use scarce hospital beds in developing countries by selecting out children with severe pneumonia for the day-care management, who following existing guidelines, would have been identified as the ones requiring hospitalization. This would be a practical approach in developing countries - a smaller investment in upgrading the day-care facilities through development of trained resources and procurement of some supporting equipment, which could pay back in a much greater way.

Rapid/fast breathing (WHO)

Rapid/fast breathing is defined as when the age-specific respiratory rates become ≥60/minute in neonates and infants aged <2 months, ≥50/minute in infants aged 2 to <12 months, and ≥40/minute in children aged 12-59 months, as shown below:

- Age < 2 months: ≥ 60/minute
- Age 2 to <12 months: ≥ 50/minute
- Age 12 months-5 years: ≥ 40/minute

(N. B. A child who is exactly 12 months old would have fast breathing if s/he breaths ≥ 40/minute. Tachypnoea is the best single predictor of pneumonia in children of all ages).

Lower chest-wall indrawing

Indrawing of the chest wall is a manifestation of reduced lung compliance resulting from the tendency of declining intra-alveolar pressure due to pneumonic consolidation or

airways obstruction. WHO recommends the use of lower chest wall indrawing as a sign of pneumonia requiring admission to hospital, defined as the inward movement of the bony structures of the lower chest wall with inspiration. Lower chest-wall indrawing is also called "subcostal indrawing"/"subcostal retractions"

Clinical types of pneumonia (WHO)
- Very severe pneumonia (up to 5 years)
- Severe pneumonia (up to 5 years)
- Pneumonia (not severe) (only for children aged 2 months to 5 years)
- No pneumonia: cough or cold (up to 5 years)

Very severe pneumonia
If a child with cough or difficult breathing has any one or more of the following danger signs, s/he is classified as having very severe pneumonia (WHO, 2005)

- Not able to drink
- Cyanosis
- Head nodding

"No danger signs" are defined as the absence of all of the following danger signs: not able to drink/feed, central cyanosis, head nodding, stridor in calm child, abnormally sleepy, convulsion, and severe clinical malnutrition.

If a child presents with severe malnutrition with any sign of pneumonia (any of the WHO defined signs of pneumonia or severe pneumonia or very severe pneumonia or crackles or bronchial breath sound in lungs or radiological pneumonia) should be considered as very severe pneumonia.

Severe pneumonia
Severe pneumonia is defined as an young infant (< 2 months) with cough or difficult breathing having fast breathing and/or lower chest-wall indrawing, or a child (2 months to 5 years) with cough or difficult breathing having only lower chest-wall indrawing.

Pneumonia (not severe)
Pneumonia (not severe) is defined as a child (2 months to 5 years) with cough or difficult breathing having only fast breathing, but no lower chest-wall indrawing, or no signs of very severe pneumonia.

Aetiology of CAP
Rational treatment for pneumonia depends on knowing the most likely pathogens in each community, as the relative frequency of different agents may vary from one geographical region to another and depends on the age of the patient, vaccination status, immunological status, relevant exposure and clinical setting at which pneumonia was acquired. Mixed bacterial and viral infections may occur in 30-40% of cases of CAP (Zar et al., 2005). *Streptococcus pneumoniae* is the most common bacterial cause of childhood pneumonia (BTS, 2002)), followed by *Haemophilus influenzae, Mycoplasma pneumoniae, Chlamydia pneumoniae,* and *Mycobacterium tuberculosis*. The less common bacterial causes are *Staphylococcus aureus,*

Bordetella pertussis, Pneumocystis jiroveci (previously known as *Pneumocystis carinii),* and *Niserria meningitidis.* In older children, when a bacterial cause is found, it is most commonly *Streptococcus pneumoniae* followed by *Mycoplasma* and *Chlamydia* (BTS, 2002). Viruses are the most common causes of pneumonia in younger children (infancy, pre-school and school age children), except neonates (BTS, 2002). In neonates, the most common causes are *Group B streptococcus beta haemolyticus* (GBB), *Escherichia coli, Klebsiella pneumoniae, Chlamydia trachomatis* (3-19 weeks), *Cytomegalovirus (CMV),* and the less common causes are *Staphylococcus aureus, Listeria monocytogenes,* and *Pseudomonas.* The common viruses are Respiratory Syncytial Virus (RSV), influenza, and parainfluenza viruses, adenovirus, and human metapneumovirus (HMV).

The spectrum and frequency of causative agents of bacterial pneumonia in severely malnourished children often differs in pneumonic children without severe malnutrition (Chisti et al., 2009).

Table 1. Causes of CAP according to various age groups and SAM

All age groups
Bacteria are the major causes of CAP in children

1. *Streptococcus pneumoniae*: commonest
2. *Haemophilus influenzae* (including Hib & nontypable strains)
3. *Staphylococcus aureus*

*Atypical bacteria**
4. *Mycoplasma pneumoniae** (> 5 years)
5. *Chlamydia pneumoniae**
6. *Chlamydia trachomatis** (3-19 weeks)
7. *Moraxella catarrhalis*

Gram-negative bacteria**
8. *Klebsiella pneumoniae***
9. *Escherichia coli***
10. *Pseudomonas***

Viruses***
11. Respiratory syncytial virus (RSV)***
12. Influenza A or B***
13. Parainfluenza virus types 1, 3***
14. Adenovirus***
15. Human metapneumovirus (HMV)***
16. Rhinovirus***
17. Coronavirus***
18. Enterovirus***
19. CMV***
20. *Pneumocystis jiroveci* (previously known as *Pneumocystis carinii)*

0-2 months
1. *Group B streptococcus*
Gram-negative bacteria**
2. *Klebsiella pneumoniae***
3. *Escherichia coli***
4. *Pseudomonas***
5. *Staphylococcus aureus*
6. *Chlamydia trachomatis**
7. *Listeria monocytogenes*
8. Viruses***
9. *Ureaplasma urealyticum*
10. *Bordetella pertussis*

2 months-5 years
1. Viruses***
2. *Streptococcus pneumoniae*
3. *Haemophilus influenzae* (including Hib & nontypable strains) (Common in developing countries where vaccination is still not widely used)
4. *Staphylococcus aureus*
5. *Mycoplasma pneumoniae**

Above 5 years
1. *Streptococcus pneumoniae*
2. *Haemophilus influenzae* (including Hib & nontypable strains)
3. *Staphylococcus aureus*
*Atypical bacteria**
4. *Mycoplasma pneumoniae**
5. *Chlamydia pneumoniae**
6. Viruses***

SAM
1. *Klebsiella pneumonia*** (26%)
2. *Staphylococcus aureus* (25%)
3. *Streptococcus pneumoniae* (18%)
4. *Escherichia coli*** (8%)
5. *Haemophilus influenzae* (including Hib) (8%)
6. *Salmonella species***
7. *Pseudomonas***
8. *Acinetobacter* species**
9. Methicillin-resistant *Staphylococcus aureus* (MRSA)
10. *Pneumocystis jiroveci* (previously known *Pneumocystis carinii*)
11. CMV***
12. Candida

(N.B. * indicates atypical bacteria ** indicates gram-negative bacteria *** indicates viruses)

Risk factors for CAP
Some risk factors for CAP are shown below (Zar et al., 2005; Chisti et al., 2009)

Host factors
- Infancy (Age <1 year)
- Prematurity
- Low birth weight (including low weight for age)
- Malnutrition
- Immunosuppression

Social/environmental
- Overcrowding
- Air pollution
- Inadequate housing
- Low socioeconomic status
- Passive exposure to tobacco smoke
- Indoor fuel exposure
- Winter season
- Lack of breast feeding
- Failure to complete immunization
- Attendance at day-care centres
- Presence of coughing sibling (s) at home

Pneumonia in SAM
The WHO defines malnutrition as "the cellular imbalance between the supply of nutrients and energy and the energy and the body's demand for them to ensure growth, maintenance, and specific functions (de Onis et al., 1993). Among the four principal causes of deaths in young children worldwide, undernutrition has been ascribed to be the cause of death in 60.7% children with diarrhoeal diseases, 52.3% of those with pneumonia (Caulfield et al., 2004). More than half of all the childhood deaths are associated with malnutrition (Rice et al., 2000). Pneumonia is common in malnourished children and frequently associated with fatal outcome (Bryce et al., 2005; Rice et al., 2000; Loeb & High, 2005; Nannan et al., 2007). Of children with malnutrition requiring hospital admission, up to two-thirds are diagnosed with pneumonia (Shimeles & Lulseged, 1994; Ahmed et al., 1999). A most recent systematic review revealed those children with pneumonia and moderate or severe malnutrition are at higher risk of death (Chisti et al., 2009). For SAM, the relative risks ranged from 2.9-121.2 with odds ratios ranged from 2.5-15.1. For moderate malnutrition, the relative risks ranged from 1.2-36.5 (Chisti et al., 2009). The clinical classification of pneumonia based on the diagnostic criteria according to the WHO guidelines should be carefully evaluated in children with SAM. A Gambian study evaluated that the respiratory rate cut-off required in malnourished children should be taken approximately 5 breaths per minute less than that in well nourished children and this finding may be related to the lower body temperatures found in severely malnourished children with pneumonia (Falade et al., 1995). Similarly, intercostal indrawing was more common and lower chest wall indrawing was less common in severely malnourished children (Falade et al., 1995; Chisti et al., 2010). In addition, lower chest wall indrawing is not sufficiently sensitive as predictors of pneumonia in SAM and no

visible clinical signs are consistently reliable for the diagnosis of pneumonia in SAM. Malnourished children may not have the strength to manifest some of these physical signs in the same manner as well nourished children (Falade et al., 1995; Chisti et al., 2010). Moreover, data from a recent systematic review suggest that a reliance on simple clinical signs will underestimate the burden of the disease and potentially delay the diagnosis of pneumonia in severely malnourished children (Chisti et al., 2009). Therefore, WHO recommends that children with SAM who present with cough, fast or difficult breathing irrespective of having clinical signs of pneumonia or not, should be treated with appropriate antibiotics to save the lives of these high-risk group of children (Falade et al., 1995).

Occult pneumonia is another entity characterized by the absence of the clinical signs and may be diagnosed by performing a chest radiograph; it may occur in SAM with dehydrating diarrhoea (Hall & Simon, 1987; Murphy et al., 2007; Bachur et al., 1999). The typical clinical signs of pneumonia may be absent in SAM due to sub-optimal inflammatory responses, reduced power of the respiratory muscles, and depletion of potassium and magnesium (Suskind et al., 1990). SAM also contributes to immune deficiency and reduced host defense.

Pneumonia with dehydrating diarrhoea

The clinical classification of pneumonia based on the diagnostic criteria according to WHO should be carefully evaluated in children presenting with dehydrating diarrhoea caused by *Vibrio cholerae*, *ETEC*, as well as rotavirus. If a child presents with severe or some degree of dehydration, then s/he would likely to have acidosis, which is responsible for the development of tachypnoea and it would be very difficult to distinguish clinically whether the increased respiratory rate is due to pneumonia, or due to acidosis, or both. In this situation, it is generally recommended to fully rehydrate the child first with IV/oral fluid (according to the type of dehydration present) within 4-6 hours and then count the respiratory rate for detecting pneumonia according to the standard WHO guideline. It is also recommended to perform a chest radiograph after full hydration of the patient for confirming the diagnosis of pneumonia.

Diagnosis of CAP

The diagnosis of CAP should be considered in any child who has an acute onset of respiratory symptoms, particularly cough, fast breathing, or difficulty in breathing. Diagnosis includes clinical evaluation, radiographic evaluation and etiological investigations to: (i) establish whether pneumonia is present; (ii) assess the severity of pneumonia; (iii) determine the clinical type of pneumonia; and (iii) determine the causative organism. In general, diagnostic investigations to determine the cause of pneumonia are indicated only in children requiring hospitalization (Zar et al., 2005). Bacterial pneumonia cannot be reliably distinguished from viral pneumonia on the basis of any single parameter: clinical, laboratory, or chest radiographic findings.

- Clinical evaluation
- Radiographic evaluation
- Aetiological investigations
- Pulse oximetry

The best objective measurement of hypoxaemia is by pulse oximetry which avoids the need for arterial blood gases. Oxygen saturation (Sao_2) measurements provide a non-invasive estimate of the arterial oxygenation (BTS, 2002). The human eye is poor in recognizing

hypoxaemia. Even under ideal conditions, skilled observers cannot consistently detect hypoxaemia until the oxygen (O_2) saturation is below 80% (Comroe & Bothello, 1947). Pulse oximetry is probably one of the most important advances in monitoring the respiratory problems and these instruments have a reasonable degree of accuracy (Jurban, 1999). The pulse oximeter is easy to use and requires no calibration. However, it requires a pulsatile signal from the patient. When using paediatric wrap around probes, the emitting and receiving diodes need to be carefully opposed. It is also highly subject to motion artifacts. To obtain a reliable reading (i) the child should be resting, still and quiet, not crying or irritable (Zar et al., 2005; BTS, 2002); (i) a good pulse signal (plethysmograph) should be obtained; and (iii) once a signal is obtained, the saturation reading should be watched over at least 30 seconds and a value recorded once an adequate stable trace is obtained (Zar et al., 2005; BTS, 2002). Pulse oximetry as a potentially useful diagnostic tool for the detection of hypoxaemia as an indicator of severe pneumonia; have not been sufficiently evaluated for the diagnosis of children with SAM (WHO, 2005). Widespread use of pulse oximetry is now recommended for monitoring children with severe pneumonia in the developing countries. Perhaps the major challenge facing pulse oximetry is whether this technology can be incorporated effectively into the diagnostic and management algorithms that can improve the efficiency of clinical management of CAP in the developing countries (Jurban, 1999).

Significance of hypoxaemia with CAP and its management

Assessment of oxygenation is important in the evaluation of a child with pneumonia and pulse oximetry should be performed in every child admitted to a hospital with CAP (Zar et al., 2005; BTS, 2002). Hypoxaemia is defined as the arterial oxygen saturation of less than 90% in room air at sea level as recorded by the pulse oximetry, which is the most serious manifestation of childhood pneumonia (Weber et al., 1997). In white patients, an S_PO_2 target of 92% resulted in a satisfactory level of oxygenation, whereas a higher S_PO_2 target of 95% was required in black patients (Jurban, 1999; Jurban & Tobin, 1990). Alternatively, no hypoxaemia is defined as the arterial oxygen saturation of ≥90% in room air as recorded by the pulse oximetry. The median prevalence of hypoxaemia in WHO-defined pneumonia requiring hospitalization (severe and very severe pneumonia) was 13% but the prevalence varied widely (Subhi, 2009). This corresponds to at least 1.5 to 2.7 million annual cases of pneumonia with hypoxaemia presenting to the health-care facilities (Subhi, 2009). WHO recommends for children older than 2 months, the use of oxygen in severe/very severe pneumonia, as ascertained by the presence of a number of clinical indicators of hypoxaemia, including cyanosis, inability to drink, severe lower chest wall indrawing, respiratory rate greater than 70 breaths per minute, grunting respiration, or head nodding (WHO, 2005). Head nodding is a movement of the head synchronous with each breath, which is caused by increased use of auxiliary muscles of respiration and therefore indicates severe respiratory distress and an important clinical sign predicting hypoxaemia (Weber et al., 1997). Only one Gambian study showed that hypoxaemia could be predicted in only half of the children by the presence of a combination of three clinical signs, such as extreme respiratory distress, cyanosis, and severely compromised general status (Weber et al., 1997). Agitation may be an indication that the child is hypoxaemic (BTS, 2002). Hypoxaemia is also a good indicator for detecting the severity of pneumonia (Wang et al., 1995; Hall et al., 1979; Shann et al., 1989). It is a common complication of childhood infections, particularly ALRI, and case fatality rate of pneumonia is inversely related to the arterial haemoglobin oxygen saturation (SaO_2)

(Onyango et al., 1993). In pneumonia - a disease that disproportionately impacts the developing countries, hypoxaemia is an important risk factor for death (Onyango et al., 1993; Duke et al. 2000), as hypoxaemic children are five times more likely to die than non-hypoxaemic children. In patients admitted with pneumonia to a general medical service, it was found that O_2 saturation <90% of at least 5 minutes duration occurred in 26% of the patients (Bowton et al., 1994). On follow-up over the next 4-7 months, those patients experiencing hypoxaemia during the first 24 hour of hospitalization had more than a threefold higher mortality than patients who did not desaturate (Bowton et al., 1994).

In the critical care setting especially for evaluating the progress of children suffering from severe pneumonia, pulse oximetry is also used as one of the most commonly employed monitoring modalities in the critical care setting especially for evaluating the progress of children suffering from severe pneumonia (Jurban, 1999). Moreover, hypoxaemia is also an important risk factor for failure to the day-care management as well as the need for future follow-up admissions (Ashraf et al., 2010). Therefore, measurement of oxygen saturation should be routinely done in all children with severe pneumonia with pulse oximetry, and those with hypoxaemia requiring prolonged oxygen therapy for more than six hours should be referred to a hospital for long-term oxygen therapy (Ashraf et al., 2010). Results of that study were consistent with earlier reports that hypoxaemia in pneumonic children are predictors of severe disease and is a risk factor for death (Onyango et al., 1993; Duke et al., 2000). Hypoxaemia has been overlooked in world-wide strategies for pneumonia control and reducing child mortality (Subhi, 2009). It is also often overlooked in the developing countries, mainly due to the low accuracy of clinical predictors and the limited availability of pulse oximetry, despite of its more accurate detection of hypoxaemia and oxygen therapy for treatment (Subhi, 2009). Many more people do not have access to the health care facilities. Oxygen therapy in developing countries continues to be a low priority on the child health agenda (Subhi, 2009). Oxygen was never mentioned in the recent publication by the WHO and UNICEF efforts to control pneumonia (Wardlaw et al., 2006). The accurate detection of hypoxaemia is important as delivery of oxygen to the hypoxaemic children may improve the outcome. Especially in a setting where oxygen has to be bought in cylinders, a pulse oximeter might be a cost effective purchase, as it allows identification of children who are in need of oxygen, and the amount of oxygen given can be titrated to the actual need of the patient, thus avoiding unnecessary wastage of valuable oxygen (Weber et al., 1997). There is now evidence that ensuring ample supplies of oxygen and promoting a routine and systematic approach of screening for hypoxaemia by using pulse oximetry is associated with improved quality of care and reduced mortality, and that the technology required to do so is affordable and sustainable in district level hospitals and day-care centres in the developing countries (Duke et al., 2000, Dobson et al., 1996; Duke et al., 2008; Dobson, 1991; Steinhoff & Black, 2007; Matai et al., 2008). Pulse oximetry would enable accurate identification of hypoxaemia and might increase the safety and cost effectiveness of this recommendation and this diagnostic tool should be included. This was demonstrated by our recent study reporting successful day-care case management of severe pneumonia using pulse oximetry as an important part of the treatment algorithm (Ashraf et al., 2008). Hypoxaemia is a very common and treatable complication of childhood pneumonia in developing countries and it is a recognized predictor of severe disease and a risk factor for death and correlates with disease severity. For home management to be safe and ethical, it is essential that only children without hypoxaemia are managed outside health-care facilities (Subhi et al., 2009).

Children with hypoxaemic pneumonia requiring prolonged oxygen therapy for more than six hours, need to be identified (which is often difficult using only clinical signs), admitted, and given supplemental oxygen for prolonged duration, and close monitoring (Ashraf et al. 2010). The measurement of SpO_2 as a regularly measured vital sign by using pulse oximetry should be incorporated as an important part of the treatment algorithm for improving the diagnosis of hypoxaemia, and categorizing the severity of pneumonia (Onyango et al., 1993; Steinhoff & Black, 2007; Lozano et al., 1994; Weber & Mulholland, 1998). For treating children with pneumonia, there is an urgent need to increase the widespread availability as well as use of pulse oximetry for monitoring patients with severe pneumonia and effective oxygen delivery systems in the developing countries.

Classification of hypoxaemia

There are two ways of classifying hypoxaemia in children: (i) WHO classification and (ii) British Thoracic Society (BTS) classification as defined below:

(i) WHO classification of hypoxaemia

Experts from WHO often classifies hypoxaemia as mild, moderate and severe as defined below:

- Mild hypoxaemia: when the arterial oxygen saturation lies between 85 to 90%, the patient is known to have mild hypoxaemia.
- Moderate hypoxaemia: when the arterial oxygen saturation lies between 80 to 85%, the patient is known to have moderate hypoxaemia.
- Severe hypoxaemia: when the arterial oxygen saturation is less than 80%, the patient is known to have severe hypoxaemia.

(ii) BTS classification of hypoxaemia

Similarly, experts from paediatric respiratory medicine in developed countries including BTS often categorized hypoxaemia as mild, moderate and severe as defined below:

- Mild hypoxaemia: when the arterial oxygen saturation lies between 88 to 92%, the patient is known to have mild hypoxaemia.
- Moderate hypoxaemia: when the arterial oxygen saturation lies between 85 to 88%, the patient is known to have moderate hypoxaemia.
- Severe hypoxaemia: when the arterial oxygen saturation is less than 85%, the patient is known to have severe hypoxaemia.

Indications for oxygen therapy

1. Hypoxaemia (oxygen saturation <90% in room air at sea level)
2. Central cyanosis
3. Severe lower chest-wall in-drawing
4. Grunting respiration
5. Restlessness (due to hypoxaemia)
6. Inability to drink or feed
7. Respiratory rate >70 breaths/min
8. Head Nodding

Management of hypoxaemia

- Oxygen should be available at any health care facility where sick children are seen regularly. Oxygen therapy reduces mortality associated with severe pneumonia. It should be given to children who are restless, who had tachypnoea with severe lower chest wall in-drawing, head nodding, cyanosis, or not tolerating oral feeds. The SpO_2 should be maintained above 92%.
- If oxygen is required infrequently then cylinders are the most practical source of oxygen. Cylinders also allow oxygen therapy to be used while the patient is transferred to a facility with more resources.
- If oxygen is used more frequently, then oxygen concentrators are the preferred source of oxygen.
- In hospitals with oxygen supplies, wall oxygen units should be available.
- Low flow meters must be available to give appropriate oxygen flow to children. In most hospitals these will be variable orifice units, but fixed orifice units may be more practical in some units.

Key messages about hypoxaemia in relation to CAP (WHO, 2009)

- Hypoxaemia is a common complication in ALRI in children, and is a strong risk factor for death.
- At least 13% of children presenting to hospitals with severe or very severe pneumonia have hypoxaemia, and the rates are much higher in some hospitals; some exceeding 50%.
- The prevalence of hypoxaemia is higher in referral hospitals than in primary care settings. Hypoxaemia is more common at higher altitude, in younger ages and in certain geographical regions.
- SpO_2 <90% is the most clinically useful definition of hypoxaemia and is considered by most clinicians as an appropriate indication for giving oxygen.
- If pulse oximetry is available only at the time of admission, screen all patients if time allows, or those patients with any clinical signs of hypoxaemia, including all children with emergency or priority signs.
- If oximetry is used at outpatient triage, screen all children with any emergency or priority signs.
- Any child with an SpO_2 <90% should receive oxygen.
- Use oximetry, at least daily, to check any patients who are already on oxygen, and screen any patient who develops any emergency signs or shows other clinical signs of deterioration.
- Explain the meaning of oximetry to parents. This will help them understand the importance of oxygen and other treatments and will involve them in their child's care.

- Children should not be discharged until their SpO_2 has been stable at 90% or more while breathing room air for at least 24 hours, until all emergency and priority signs have resolved, and until appropriate home treatment can be organized.

Methods of oxygen administration

- Nasal prongs: are recommended for most children. Nasal prongs give a maximum fractional concentration of inspired oxygen (F_1O_2) of 28-35% except in small infants when higher concentrations may be obtained. This method does not require humidification of oxygen and ensures that the child receives oxygen during feeding. Oxygen flow rates of 0.5-1 l/minute are required in children less than 2 months old and 2-3 l/minute in infants and children aged 2 months to 5 years.
- Nasal catheters: are usually well tolerated and humidification is not required, but they can be blocked by mucous. Oxygen via nasal catheters gives a maximum F_1O_2 of 35-40%.
- Nasopharyngeal catheters: have the advantage of requiring the lowest flow rate to achieve a given oxygen concentration in the airways. Infants under the age of 2 months can usually be treated with 0.5 minute and infants up to 1 year with 1 minute. However, humidification of oxygen is required and the catheter may be easily blocked. Further, potentially lethal complications including gastric distension, airway obstruction, apnoea, pneumo-orbitus and pneumocephalus may occur. Continuous skilled nursing is therefore necessary to prevent these complications. Consequently, oxygen administration via nasopharyngeal catheter is not recommended.
- Headbox: oxygen is well tolerated by young infants. Headbox oxygen requires no humidification but requires a high flow and a mixing device to ensure the correct F_1O_2 is delivered. This is the *least preferred* method as there is wastage of oxygen and delivered F_1O_2 is unpredictable.
- Facemask: oxygen is designed to deliver 28%-65% oxygen at a flow rate of 6-10 minutes.
- Polymask: In severely hypoxaemic infants who are not ventilated, oxygen should be administered using a polymask whereby F_1O_2 concentrations of 60-80% may be achieved. The flow rate should be regulated to keep the bag of the mask inflated during inspiration and expiration.
- Using the prone position for infants may improve hypoxaemia and the respiratory system compliance (Chaisupamongkollarp et al., 1999) and should be attempted if hypoxaemia is difficult to treat.
- Oxygen should be discontinued when the child is improving and the transcutanous saturation is above 90% in room air, as recorded by the pulse oximetry.

Radiological diagnosis

Radiological changes may be vague or inconclusive or even absent despite the presence of clinical signs of pneumonia (Doherty, 1991; Hamid et al., 1996; Wafula et al., 1998: Chisti et al., 2009). Conversely, clinical signs of pneumonia can be absent in the presence of radiological signs of pneumonia (Murphy et al., 2007; Bachur et al., 1999; Chisti et al., 2009). There are two main clinical definitions of pneumonia based on the radiological findings:

Bronchopneumonia is defined as a febrile illness with cough, respiratory distress with evidence of localized or more than one or generalized patchy infiltrates on the chest x-ray.

Lobar pneumonia is defined as a febrile illness with cough, respiratory distress with an illness similar to that of bronchopneumonia, except that the physical findings (affected lobe reveals woody dull on percussion, rales, increased vocal resonance and/or bronchial breath sound on auscultation) and radiographic examination indicate lobar consolidation.

Occult pneumonia: It was observed that approximately 25% of the febrile children defined as the rectal temperature becoming more than 38^0 Celsius (Ashraf et al., 2010), with a WBC count >20,000/mm^3, but without any lower respiratory tract findings on examination, had radiographic evidence of pneumonia, known as occult pneumonia, commonly found in children with SAM and children with dehydrating diarrhoea (Murphy et al., 2007; Bachur et al., 1999; Chisti et al., 2009).

Limitations of chest radiography

- Less useful in discriminating the causative pathogens
- Cannot accurately discriminate viral from bacterial pneumonias (Swingler, 2000).
- Wide range of inter- and intra-observer variation in the interpretation (Swingler, 2001; Bada et al., 2007; Pauls et al., 2007; Sarria et al., 2003), not only among the paediatricians, but also among the radiologists, even paediatric radiologists
- Does not result in the improved outcome or change in the treatment of ambulatory settings (Swingler et al., 2000)

Indications for CXR

- To confirm the presence of pneumonia
- To detect clinical pneumonia, unresponsive to the standard ambulatory management
- To identify suspected cavitations or military mottling in PTB
- To identify suspected foreign body aspiration
- To identify hospitalized children for the detection of local complications of pneumonia, such as pleural effusion, pneumothorax, empyema thoracis, advanced stage of bronchiectasis, and lung abscess
- High fever, leukocytosis with no obvious focus of infections (26% such cases may have radiographic pneumonia) (Bachur et al., 1999).
- Children developing secondary heart failure
- Children with congenital problems, such as Congenital Heart Disease (CHD), cystic fibrosis, Down's Syndrome
- Children with re-current attacks of pneumonia

Indications for follow-up CXR

- Children with lobar collapse
- To document the resolution of a round pneumonia (as this may mimic the appearance of a Ghon focus)
- Children with ongoing respiratory symptoms
- Children with re-current attacks of pneumonia

General tests of infection
They may not be useful to differentiate bacterial from viral pneumonia (Nohynek et al., 1995; Toikka et al., 2000; Korppi et al., 2003)

● WBC count, neutrophil count (PMN leukocytosis suggests bacterial pneumonia (Marks & Klein, 1995; Klein, 1992) and lymphocytic leukopenia suggests viral pneumonia) (Austrian & Gold, 1964)
● C-reactive protein (>40 mg suggests bacterial infection)
● ESR
● Procalcitonin
● Copeptin
● Blood culture: to identify the causative bacterial pathogen, that is possible in only less than 30% (10-30%) of cases of CAP (Donowitz & Mandell, 1990), and to determine its sensitivity
● Pleural fluid: if present, should be aspirated and investigated for specific infectious agents

The C-reactive protein, ESR, procalcitonin, and copeptin are the non-specific markers for the diagnosis of pneumonia.

Indications for hospital admission
1. Hypoxaemia (oxygen saturation <90% in room air at sea level)
2. Toxic appearance
3. Respiratory rate >70/minute, or severe respiratory distress
4. Infants < 2 months
5. Impaired level of consciousness
6. Inability to drink or eat
7. Cyanosis
8. Stridor in calm child
9. Chronic lung disease
10. Systemic manifestation
11. Intermittent apnoea
12. Grunting respiration
13. Severe lower chest-wall indrawing
14. SAM
15. Family unable to provide adequate care/non-compliant parents
16. Failure to respond ambulatory care/no response to previous oral antimicrobial therapy
17. Clinical deterioration on treatment
18. Immunocompromised host/immunodeficiency
19. Recurrent pneumonia

Indications for transfer and admission to Paediatric Intensive Care Unit (PICU)

1. Needs ventilator support
2. Failure to maintain a saturation of >90% with oxygen therapy
3. Apnoea or slow irregular breathing
4. Severely acidotic patient
5. Exhaustion with rising respiratory rate and pulse rate
6. Patient is in shock

Differential diagnosis of a child with cough, or difficult breathing

Diagnosis	Points in favour
1. Pneumonia	Fast breathing Lower chest wall indrawing Crepitations on auscultation Bronchial breathing Nasal flaring Grunting respiration Head nodding
2. Cardiac failure	Tachycardia Tachypnoea Enlarged tender liver Dependent oedema Raised jugular venous pressure Central cyanosis Heart murmur Gallop rhythm
3. Pneumothorax	Sudden onset Sudden onset of unexplained tachypnoea and respiratory distress (disproportionate to the severity of pneumonia) Hyper-resonance chest on the affected side on percussion Shift of mediastinum (trachea, apex beat to opposite side) Diminished or absent breath sound on auscultation on the affected side
4. Pleural effusion, empyaema	Stony dull on percussion (it is difficult to elicit in young child) Diminished breath sound on the affected side of lesion Shift of mediastinum (trachea, apex beat to opposite side)
5. Pericardial effusion	Oedema feet Raised jugular venous pressure Apex beat not visible/not palpable Increased area of cardiac dullness

Heart sound (muffled or absent)
Pulsus paradoxus
Enlarged liver

Pneumonia in older children often present in many ways
The following two classic presentations have been described for pneumonia (Jadavi et al., 1997)

Typical presentation (predominantly respiratory signs)

- Fever
- Chills
- Pleuritic chest pain
- Productive cough
- Fast breathing
- Lower chest wall indrawing
- Cyanosis

Atypical presentations (single or in combinations) gradual onset over several days to weeks:

- Nonproductive cough
- Low-grade fever
- Headache
- Malaise
- Meningism
- Acute abdominal pain
- Acute pain in chest or shoulder
- Convulsion

Antibiotic use in the treatment of CAP
When treating CAP, the clinical, laboratory and radiographic findings should be considered, especially when the child is hospitalized. As it is difficult to distinguish bacterial from viral pneumonia and because of the frequency of mixed bacterial-viral infections (≈30-40%) (Zar et al., 2005), all children with CAP would require an antibiotic. The age of the child, nutritional status, immunologic status of the host, local epidemiology of respiratory pathogens, and sensitivity of these pathogens to particular antimicrobial agents and the emergence of antimicrobial resistance usually play a big role to determine the choice of antibiotic therapy. The severity of pneumonia and the drug costs also have a great impact on the selection of antimicrobial therapy, particularly in the developing countries. The management of a child with CAP involves a number of decisions regarding treatment with antibiotics (BTS, 2002).

- Whether to treat with antibiotics?
- Which antibiotic and by which route?
- When to change to oral treatment?
- Total duration of antibiotic therapy;
- When to change antibiotic and why?

Outpatient management

In children with mild pneumonia (non-severe pneumonia), the breathing is fast, but there is no lower chest wall indrawing. Oral antibiotics at an appropriate dose for an adequate duration are effective for treatment. The mother is advised to return in two days for reassessment, or earlier if the child appears to deteriorate.

Antimicrobial agent	Recommended dosage	Route	Comment
Neonate (0-4 weeks)			
Ampicillin plus Gentamicin	100 mg/kg/day 12 hourly 6 mg/kg/day 12 hourly	I/V I/V	1st line of treatment
Ceftazidime plus Flucloxacillin	75-100 mg/kg/day 8 hrly 100 mg/kg/day 6 hourly	I/V I/V	2nd line of treatment
Infants > 4-8 weeks			
Ampicillin plus Gentamicin	100 mg/kg/day 6 hourly 6 mg/kg/day 12 hourly	I/V I/V	1st line of treatment
Ceftriaxone plus Gentamicin	75-100 mg/kg/day od 6 mg/kg/day 12 hourly	I/V I/V	2nd line of treatment
Infants >8 weeks to children of 5 years plus above 5 years			
Amoxicillin	100 mg/kg/day 8 hourly	Oral	1st line of treatment
Azithromycin	10 mg/kg/day once daily	Oral	2nd line of treatment
Ceftriaxone	75-100 mg/kg/day od	I/V	3rd line of treatment
Severe pneumonia with SAM			
Ampicillin plus Gentamicin	100 mg/kg/day 6 hourly 6 mg/kg/day 12 hourly	I/V I/V	1st line of treatment
Ceftriaxone plus Gentamicin	75-100 mg/kg/day od 6 mg/kg/day 12 hourly	I/V I/V	2nd line of treatment
Ceftazidime plus Flucloxacillin	75-100 mg/kg/day 8 hrly 100 mg/kg/day 6 hourly	I/V I/V	3rd line of treatment
Suspected Staph aureus pneumonia			
Amoxicillin plus Flucloxacillin (Oxacillin/ Nafcillin for MRSA)	100 mg/kg/day 8 hourly 100 mg/kg/day 6 hourly	I/V I/V	1st line of treatment
Ceftriaxone plus Flucloxacillin (Clindamicin/Vancomycin for MRSA)	75-100 mg/kg/day od 100 mg/kg/day 6 hourly	I/V I/V	2nd line of treatment
Vancomycin	10 mg/kg iv 8 hourly	I/V	3rd line of treatment

Table 2. Antimicrobial treatment of CAP

Suspected pseudomonas pneumonia			
Ceftazidime plus Ciprofloxacillin	100 mg/kg/day 8 hrly 20 mg/kg/day 12 hourly	I/V I/V	1st line of treatment
Suspected PCP pneumonia			
Co-trimoxazole (SXT)	20 mg/kg loading dose followed by 10 mg/kg in 2 divided doses or, 20 mg/kg/day in 4 divided doses	Oral	1st line of treatment. Therapy to be continued for at least 14 days (sometimes 21 days)
Suspected hospital acquired pneumonia			
a) For early onset HAI (if HAI occurs < 96 hours of admission)			
Fluroquinolone (e.g. Ciprofloxacin) plus aminoglycosides (e.g. Gentamicin)	20 mg/kg/day in 2 divided doses 6 mg/kg/day 12 hourly	I/V I/V	1st line of treatment
3rd generation cephalosporin e. g. Ceftriaxone Monotherapy with Fluroquinolone	75-100 mg/kg/day od 6 mg/kg/day 12 hourly	I/V I/V	2nd line of treatment (HAI where we don't suspect *Staph*)
3rd generation cephalosporin e. g. Ceftriaxone plus Flucloxacillin	75-100 mg/kg/day od 100 mg/kg/day 6 hourly	I/V I/V	3rd line of treatment (HAI where we suspect *Staph*)
b) For late onset HAI (if HAI occurs > 96 hours of admission)			
Anti-pseudomonal penicillin (e. g. Ticarcillin/clavulanic acid) plus Anti-MRSA (e. g. Vancomycin)	50 mg/kg/dose (Ticarcillin base: max. 3.0 gm/dose) 6 hourly 10 mg/kg iv 8 hourly	I/V I/V	1st line of treatment
Anti-pseudomonal cephalosporin (e. g. Ceftazidime) plus Aminoglycosides with wide coverage (e.g. Amikacin), or Anti-MRSA (e. g. Vancomycin)	75-100 mg/kg/day 8 hrly 6 mg/kg/day 12 hourly 10 mg/kg iv 8 hourly	I/V I/V I/V	2nd line of treatment

Duration of antibiotic treatment

Antibiotic therapy is generally recommended for 5 to 7 days for uncomplicated cases of childhood pneumonia (Zar et al., 2005; Mehta, 2003). For suspected *Staphylococcus aureus* infection, the duration of treatment may be extended for 14 to 21 days, depending on the clinical response. Gram-negative bacilli, or *Legionella* species, may also require longer courses of therapy for 10 to 21 days (BTS, 2002; Mehta, 2003). Alternatively, the newer macrolides such as azithromycin may be used for 3-5 days (Zar et al., 2005). In case of neonates, the treatment should be continued for at least 2 weeks. If pneumonia is complicated with empyema, the treatment should be continued for at least 4 weeks.

Switching from parenteral therapy to oral therapy is a key management issue for childhood pneumonia. Children receiving parenteral therapy for 2 to 4 days can usually be switched to oral therapy provided there is clinical improvement as children becoming afebrile defined as the rectal temperature becoming 38^0 Celsius or less and remaining so for at least 24 hours (Ashraf et al., 2010), they can tolerate medication orally, they do not have any diarrhoea and vomiting and have no relevant local complications of pneumonia (Shalit et al., 1994; Dagan et al., 1994). Switching over to oral antibiotics will help for early discharge from the hospital and subsequently prevent hospital acquired infection and vacant hospital beds for other sick children.

Indications for the use of antipyretics and analgesics in CAP

- Rectal temperature >39^0 Celsius
- There is a known risk of febrile convulsions
- There is central nervous system pathology that may be aggravated by high fever

Children with CAP are generally pyrexial and may also have some pain, including headache, chest pain, arthralgia (in cases of *Mycoplasma pneumonia*e), referred abdominal pain, and possibly earache from associated otitis media. Pleural pain may interfere with the depth of breathing and may impair the ability of the child to cough. Antipyretics and analgesics can be used to keep the child comfortable and to help coughing. Minimal handling helps to reduce metabolic and oxygen requirements and this should be considered when planning and carrying out procedures, investigations, and treatments. Pain associated with pneumonia may be due to pleurisy or to pathology involving the upper airways. Pain or discomfort should be treated as it may severely compromise respiratory function and adequate clearance of secretions. The most appropriate agent is paracetamol at a dose of 15 mg/kg/dose given 4-6-hourly orally or 20-40 mg/kg/dose per-rectally for two-three times daily. If this dose does not provide adequate analgesia, a mixture of paracetamol and codeine (0.5 mg/kg/dose 8-hourly) is very effective. Aspirin is contraindicated in most children because of the association with Reye's syndrome (Zar et al., 2005).

Calorie requirements

Adequate nutrition is of particular concern, especially when there are underlying factors such as malnutrition. A minimum of 50-60 kcal/kg/day should be given to a child with pneumonia with continuation of regular breast feeding for breast-fed children. A calorie intake of 80-100 kcal/kg/day should be given to a non-breast fed child with CAP. Ensuring adequate calorie intake is essential as there is an excessive demand on the energy reserves in children with pneumonia, in whom the work of breathing is increased. Children should not be starved for more than 24 hours to prevent the development of hypoglycaemia. In the presence of malnutrition, and following several days of poor nutrition, this needs to be increased considerably. In the early phase of pneumonia, ketosis should be avoided by ensuring adequate carbohydrate intake. With time, a greater proportion of intake can be lipids. The intake of calories should be adequate to meet the metabolic requirements and to promote growth.

Enteral feeds
Children with pneumonia should be encouraged to feed orally unless there are indications for nasogastric feeding/intravenous fluid infusions. If children are too distressed to take fluid and feeds orally, continuous enteral feeds via a nasogastric tube may be provided.

Indications for N/G tube feeding
- Too distressed to drink or swallow safely
- Having frequent severe coughing episodes that may be associated with vomiting and possible aspiration of gastric contents
- Hypovolaemia with associated poor peripheral perfusion (may even require I/V fluid)
- Painful oral sore/condition which interfere with feeding by mouth

Fluid therapy
Children with uncomplicated pneumonia should receive normal maintenance fluids. Appropriate rehydration is required in children who are dehydrated. Oral intake should cease when a child is in severe respiratory distress. In severe pneumonia, inappropriate secretion of anti-diuretic hormone (ADH) is increased (Dhawan et al., 1992), dehydration is therefore uncommon. It is important that the child should not be over hydrated. A study of 264 hospitalized children with CAP in India has shown hyponatraemia on admission in 27% cases and it was calculated that, in 68% of these children, the hyponatraemia was secondary to inappropriate ADH secretion (SIADH) (Singhi & Dhawan, 1992). Treatment is with fluid restriction.

Intravenous fluids must be used with great care and with caution, and only if adequate monitoring is available (Zar et al., 2005). Children who are vomiting or who are severely ill may require intravenous fluids. These should be given at 80% of the basal levels (once hypovolaemia has been corrected). In children with severe or complicated pneumonia, serum urea and electrolytes should be measured before instituting I/V fluids as among them (SIADH) is common. In these children, fluid intake should be restricted to 40-60% of normal requirements, i.e. 50 ml/kg/day of I/V fluids. They should be frequently monitored as severely ill children with CAP might develop SIADH as a recognized complication (Dhawan et al., 1992; Singhi & Dhawan, 1992).

Indications for I/V fluid
- Shock
- Inability to tolerate enteral feeds
- Sepsis
- Severe dehydration
- Gross electrolyte imbalance
- Hypoglycaemia

Monitoring of the child with CAP
The following parameters should be routinely monitored in every child with CAP, the frequency of which will depend on the severity of illness as well as the availability of

resources. Special attention should be given to child receiving I/V fluid therapy and those with SAM.

- Heart rate
- Respiratory rate
- Temperature
- Respiratory pattern including chest recession
- Lower chest wall indrawing
- Use of accessory muscles
- Establishment of oral feeding
- Liver size
- Oxygen saturation level
- Chest auscultation: rales, rhonchi, bilateral basal crepitation, pleural rub
- Fluid and calorie intake

Children on oxygen therapy should have at least 4-hourly observations of all the above parameters and children without getting oxygen should be observed at least 12-hourly. If a child remains pyrexial or unwell 48 hours after admission with pneumonia, re-evaluation is necessary with consideration given to exclude possible local complications of CAP (BTS, 2002).

Micronutrient supplementation
In children with CAP, as an adjuvant therapy with antibiotics, 20 mg of Zinc po daily until discharge was found to accelerate the recovery from severe pneumonia, reducing the duration of hypoxaemia (Brooks et al., 2004; Shakur et al., 2004; Mahalanabis et al., 2002). Zinc should therefore be considered for use in children hospitalized with CAP, particularly if there is co-existing SAM. Zinc also reduces the incidence of pneumonia, especially in children with SAM. But, studies from Vellore, India showed that zinc has no significant role to reduce the morbidity and mortality in children with acute severe pneumonia (Bose et al., 2006). Zinc should therefore be considered cautiously for use in children hospitalized with CAP.

Non-response to therapy
If a child remains pyrexial or unwell 48 hours after admission with CAP, re-evaluation is necessary with consideration given to the possible complications:

- Inappropriate drug (antibiotic): in relation to choice of antibiotic, adequate dosage, route of administration, and duration of antibiotic therapy
- Development of local lung complications of CAP such as pleural effusion, empyema, lung abscess, bronchieactasis, pneumothorax, liver abscess etc.
- Immunosuppression
- Coexisting disease such as cystic fibrosis, chronic suppurative bronchitis, congenital heart disease (CHD), Down's Syndrome
- Underlying SAM: slow, delayed and poor response to conventional antibiotic therapy
- Underlying TB (PTB, miliary TB, disseminated TB, TBM)

- Underlying malignancy
- Underlying HIV infection
- Development of heart failure
- Metastatic infection can rarely occur as a result of the septicaemia associated with CAP. Osteomyelitis or septic arthritis should be considered, particularly with *Staph aureus* infections.
- Incorrect diagnosis of CAP

Complications of CAP

- Fortunately, most children with CAP recover without any complication
- Persistent effusions and empyemas are the most common serious complications of bacterial pneumonia
- Pulmonary abscess
- Respiratory distress
- Sepsis (bacteraemia may occur in 10-30% cases of pneumonia; sepsis in <10% cases especially in SAM)
- Tension pneumothorax (very rare: less than 1%)

Patient education

- Parents should be cautioned to look for the signs of increasing respiratory distress, danger signs of very severe pneumonia, clinical signs of hypoxaemia and advised to seek medical attention immediately if any of these signs appear
- Most children with CAP treated with outpatient antibiotics will be much improved within 48 hours after the initiation of treatment. If such improvement does not occur, medical attention should be sought.

Medicolegal Pitfalls

- Attempting to treat neonates and very young infants on an outpatient basis
- Failure to recognize and treat signs of respiratory compromise, heart failure, and sepsis
- Failure to recognize and treat associated SAM
- Failure to give parents clear discharge instructions

Measures of *no value* in the treatment of CAP

- Chest physiotherapy: The function of chest physiotherapy is to assist the removal of tracheobronchial secretions resulting in an increase of gas exchange and reduction in work of breathing. However, trials have found no clinically discernible benefit or impact of chest physiotherapy on the course of illness in bronchiectasis, cystic fibrosis, pneumonia, bronchiolitis, asthma, acute atelectasis, inhaled foreign body and post extubation babies. There is no evidence to support the use of chest physiotherapy including postural drainage, percussion of the chest, or deep breathing exercises that should be routinely performed in children with uncomplicated CAP (Levine, 1978; Britton et al., 1985; Stapleton, 1985; Wallis & Prasad, 1999). There is a suggestion that physiotherapy is counterproductive, with patients who receive chest physiotherapy being at risk of having a longer duration of fever than the control group (Britton et al., 1985). In addition, there is also no

evidence to show that physiotherapy is beneficial in the resolving stage of pneumonia (Wallis & Prasad, 1999). Therefore, chest physiotherapy is not beneficial and should NOT be routinely prescribed for children with CAP. A supported sitting position may help to expand the lungs and improve the respiratory symptoms in children with respiratory distress. Chest physiotherapy only works in children with pneumonia having chronic lung disease (cystic fibrosis, suppurative chronic lung disease, primary ciliary dyskinesia).

- Mucolytic agents: Anti-tussive remedies are not recommended as they cause suppression of cough and interfere with airway clearance. Adverse effects and overdose have been reported. Therefore, they should not be advised in children with CAP.
- Postural drainage: There is no evidence for the use of a head-down position for postural drainage.
- Nebulized bronchodilators: Nebulized bronchodilators or saline do not improve the outcome of CAP.
- Cortocosteroids: There is no evidence to support the use of oral or inhaled corticosteroids in CAP.

References

Ahmed T, Ali M, Ullah MM et al. Mortality in severely malnourished children with diarrhoea and use of a standardised management protocol. Lancet 1999;353:1919-22.

Ashraf H, Ahmed T, Hossain MI, Alam NH, Mahmud R, Kamal SM, Salam MA, Fuchs GJ. Day-care management of children with severe malnutrition in an urban health clinic in Dhaka, Bangladesh. J Trop Pediatr 2007;53:171-8.

Ashraf H, Jahan SA, Alam NH, Mahmud R, Kamal SM, Salam MA, Gyr N. Day-care management of severe and very severe pneumonia, without associated co-morbidities such as severe malnutrition, in an urban health clinic in Dhaka, Bangladesh. Arch Dis Child 2008;93:490-4.

Ashraf H, Mahmud R, Alam NH, Jahan SA, Kamal SM, Haque F, Salam MA, Gyr N. Randomized-controlled trial of day-care vs hospital-care management of severe childhood pneumonia in Bangladesh. Pediatr (in press).

Austrian R, Gold J. Pneumococcal bacteraemia with especial reference to bacteremic pneumococcal pneumonia. Ann Intern Med 1964;60:759-76.

Bachur R, Perry H, Harper MB. Occult pneumonias: empiric chest radiographs in febrile children with leukocytosis. Ann Emerg Med 1999;33:166-73.

Bada C, Carreazo NY, Chalco JP, Huicho L. Interobserver agreement in interpreting chest X-rays on children with acute lower respiratory tract infections and concurrent wheezing. Sao Paulo Medical Journal 2007;125:150-4.

Baqui AH, Black RE, Arifeen SE, Hill K, Mitra SN, al Sabir A. Causes of childhood deaths in Bangladesh: results of a nationwide verbal autopsy study. Bull World Health Organ 1998;76:161-71.

Berman S, McIntosh K. Selective primary health care: strategies for control of disease in the developing world. XXI. Acute respiratory infections. Rev Infect Dis 1985;7:674-91.

Bose A, Coles CL, Gunavathi, John H, Moses P, Raghupathy P, Kirubakaran C, Black RE, Brooks WA, Santosham M. Efficacy of zinc in the treatment of severe pneumonia in hospitalized children <2 y old. Am J Clin Nutr 2006;83:1089-96.

Bowton DL, Scuderi PE, Haponik EF. The incidence and effect on outcome of hypoxemia in hospitalized medical patients. Am J Med 1994;97:38-46.

British Thoracic Society Standards of Care Committee. BTS Guidelines for the Management of Community Acquired Pneumonia in Childhood. Thorax 2002;57:1-24.

Britton S, Bejstedt M, Vedin L. Chest physiotherapy in primary pneumonia. BMJ (Clin Res Ed) 1985;290:1703-5.

Brooks WA, Yunus M, Santosham M, et al. Zinc for severe pneumonia in very young children: double-blind placebo-controlled trial. Lancet 2004;363:1683-88.

Bryce J, Boschi-Pinto C, Shibuya K, Black RE. WHO estimates of the causes of death in children. Lancet 2005;365:1147-52.

Bulla A, Hitze KL. Acute respiratory infections: a review. Bull World Health Organ 1978;56:481-98.

Cashat-Cruz M, Morales-Aguirre JJ, Mendoza-Azpiri M. Respiratory tract infections in children in developing countries. Semin Pediatr Infect Dis 2005;16:84-92.

Caulfield LE, de Onis M, Blossner M, et al. Undernutrition as an underlying cause of child deaths associated with diarrhea, pneumonia, malaria, and measles. Am J Clin Nutr 2004;80:193-8.

Chaisupamongkollarp T, Preuthipan A, Vaicheeta S, Chantarojanasiri T, KongvivekkajornkijW, Suwanjutha S. Prone position in spontaneously breathing infants with pneumonia. Acta Paediatr 1999;88:1033-4.

Chisti MJ, Tebruegge M, Vincente SL, Graham SM, Duke T. Pneumonia in severely malnourished chidren in developing countries - mortality risk, aetiology and validity of WHO clinical signs: a systematic review. Trop Med Inter Health 2009;14:1173-89.

Chisti MJ, Salam MA, Sharifuzzaman, Pietroni MAC. Occult pneumonia: an unusual but perilous entity presenting with severe malnutrition and dehydrating diarrhoea. J Health Popul Nutr 2009:27:808-12.

Chisti MJ, Ahmed T, Faruque AS, Salam MA. Clinical and laboratory features of radiologic pneumonia in severely malnourished infants attending an urban diarrhoea treatment center in Bangladesh. Pediatr Infect Dis J 2010;29:174-7.

Comroe JH, Bothello S. The unreliability of cyanosis in the recognition of arterial anoxemia. Am J Med Sci 1947;214:1-9.

Dagan R, Syrogiannopoula G, Ashkenazi S, et al. Parenteral-oral switch in the management of paediatric pneumonia. Drugs 1994;47:43-51.

de Onis M, Monterio C, Clugston G. The worldwide magnitude of protein energy malnutrition: an overview from the WHO global database on child growth. Bull World Health Organ 1993;71:703-12.

Dhawan A, Narang A, Singhi S. Hyponatraemia and the inappropriate ADH syndrome in pneumonia. Ann Trop Paediatr 1992;12:455-62.

Dobson MB. Oxygen concentrators offer cost savings for developing countries: a study based in Papua New Guinea. Anaesthesia 1991;146:217-9.

Dobson M, Peel D, Khallaf N. Field trial of oxygen concentrations in upper Egypt. Lancet 1996;347:1597-9.

Doherty J. WHO guidelines on detecting pneumonia in children. Lancet 1991;338:1454.

Donowitz GR, Mandell GL. Acute pneumonia. In: Mandell GL, Douglas RG, Bennet JE, editors. Principles and practice of infectious diseases. New York: Churchill Livingstone;1990:540-54.

Duke T, Frank D, Mgone J. Hypoxaemia in children with severe pneumonia in Papua New Guinea. Int J TB Lung Dis 2000;5:511-9.

Duke T, Tamburlini G. The Paediatric Quality Care Group. Improving the quality of paediatric care in peripheral hospitals in developing countries. Arch Dis Child 2003;88:563-5.

Duke T, Wandi F, Jonathan M, et al. Impact of improved oxygen systems on child deaths from pneumonia: a multi-hospital effectiveness study in Papua New Guinea. Lancet 2008;372:1328-33.

Falade AG, Tschappeler H, Greenwood BM, Mulholland EK. Use of simple clinical signs to predict pneumonia in young Gambian children: the influence of malnutrition. Bulletin of the World Health Organization 1995;73:299-304.

Garenne M, Ronsmans C, Campbell H. The magnitude of mortality from acute respiratory infections in children under 5 years in developing countries. World Health Stat Q 1992;45:180-91.

Graham SM, English M, Hazir T, Enarson P, Duke T. Challenges to improving case management of childhood pneumonia at health facilities in resource-limited settings. Bull World Health Organ 2008;86:349-55.

Hall CB, Hall WJ, Speers DM. Clinical and physiological manifestations of bronchiolitis and pneumonia. Outcome of respiratory syncytial virus. Am J Dis Child 1979;133:798-802.

Hall FM, Simon M. Occult pneumonia associated with dehydration: myth or reality. Am J Roentgenol 1987;148:853-4.

Hamid M, Qazi SA, Khan MA. Clinical, nutritional and radiological features of pneumonia. Journal of the Pakistan Medical Association 1996;46:95-9.

Huq F, Rahman M, Nahar N, Alam A, Haque M, Sack DA, Butler T, Haider R. Acute lower respiratory tract infection due to virus among hospitalized children in Dhaka, Bangladesh. Rev Infect Dis 1990:12 Suppl 8:S982-7.

Jadavi T, Law B, Lebel MH, Kennedy WA, Gold R, Wang EEL. A practical guide for the diagnosis and t treatment of pediatric pneumonia. Can Med Assoc J 1997;156:S703-S711.

Jurban A, Tobin MJ: Reliability of pulse oximetry in titrating supplemental oxygen therapy in ventilator- dependent patients. Chest 1990;97:1420-5.

Jubran A. Pulse oximetry. Crit Care 1999; 3:R11-R17.

Klein JO. Bacterial pneumonias. In: Textbook of pediatric infectious diseases. 3rd ed. Philadelphia: WB Saunders;1992:299-314.

Korppi M, Remes S, Heiskanen-Kosma T. Serum, procalcitonin concentrations in bacterial pneumonia in children: a negative result in primary healthcare settings. Pediatr pulmonol 2003;35:56-61.

Levine A. Chest physiotherapy for children with pneumonia. J Am Osteopath Assoc 1978;78:122-5.

Loeb M, High K. The effect of malnutrition on risk and outcome of community-acquired pneumonia. Respiratory Care Clinics of North America 2005;11:99-108.

Lozano JM, Steinhoff M, Ruiz JG, Mesa ML, Martinez N, Dussan B. Clinical predictors of acute radiological pneumonia and hypoxaemia at high altitude. Arch Dis Child 1994;71:323-27.

Mahalanabis D, Chowdhury A, Jana S, et al. Zinc supplementation as adjunct therapy in children with measles accompanied by pneumonia: a double-blind randomized controlled trial. A J Clin Nutr 2002;76:604-7.

Marks MI, Klein JO. Bacterial infections of the respiratory tract. In: Feigin RD, Cherry JD, editors. Infectious diseases of the fetus and newborn infant. 4th ed. Philadelphia: WB Saunders;1995:891-908.

Matai S, Peel D, Jonathan M, Wandi F, Subhi R, Duke T. Implementing an oxygen programme in hospitals in Papua New Guinea. Ann Trop Paediatr 2008;28:71-8.

Mehta PN. Choosing antibiotics for community acquired pneumonia. Indian Pediatr 2003;40:958-64.

Mulholland K. Magnitude of the problem of childhood pneumonia. Lancet 1999;354:590-2.

Murphy CG, van de Pol AC, Harper MB, Bachur RG. Clinical predictors of occult pneumonia in the febrile child. Acad Emer Med 2007;14:243-9.

Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. Lancet 1997;349:1269-76.

Nohynek H, Valkeila E, Leinonen M, et al. Erythrocyte sedimentation rate, white blood cell count and serum C-reactive protein in assessing etiologic diagnosis of acute lower respiratory infections in children. Pediatr Infect dis J 1995;14:484-90.

Nannan N, Norman R, Hendricks M, Dhansay MA, Bradshaw D. Estimating the burden of disease attributable to childhood and maternal undernutrition in South Africa in 2000. South African Medical Journal 2007;97:733-9.

Onyango FE, Steinhoff MC, Wafula EM, Wariua S, Musia J, Kitonyi J. Hypoxaemia in young Kenyan children with acute lower respiratory infection. BMJ 1993;306:612-5.

Pauls S, Kruger S, Richter K, et al. Interobserver agreement in the assessment of pulmonary infiltrates on chest radiography in community-acquired pneumonia. Rofo-Fortschritte auf dem Gebieta der Rontgenstrahlen und der Nuklearmedinn 2007;79;1152-8.

Rahman M, Huq F, Sack DA, Butler T, Azad AK, Alam A, Nahar N, Islam M. Acute lower respiratory tract infections in hospitalized patients with diarrhea in Dhaka, Bangladesh. Rev Infect Dis 1990:12 Suppl 8:S899-906.

Rice AL, Sacco L, Hyder A, Black RE. Malnutrition as an underlying cause of childhood deaths associated with infectious diseases in developing countries. Bull World Health Organ 2000;78:1207-21.

Riley I, Carrad E, Gratten H, et al. The status of research in acute respiratory infections in children in Papua New Guinea. Pediatr Res 1983;17:1041-3.

Rudan I, Tomaskovic L, Boschi-Pinto C, Campbell H, WHO Child Health Epidemiology Reference Group. Global estimate of the incidence of clinical pneumonia among children under five years of age. Bull World Health Organ 2004;82:895-903.

Rudan R, Boschi-Pinto C, Biloglav Z, Mulholland K, Campbell H. Epidemiology and etiology of childhood pneumonia. Bull World Health Organ 2008;86:408-16.

Sarria E, Fisher GB, Lima JA, Menna Barreto SS, Flores JA, Sukiennik R. Interobserver agreement in the radiological diagnosis of lower respiratory tract infections in children. J Pediatr (Rio J) 2003;79:497-503.

Sazawal S, Black RE. Pneumonia Case Management Trials Group. Effect of pneumonia case management on mortality in neonates, infants, and preschool children: a meta-analysis of community-based trials. Lancet Infect Dis 2003;3:547-56.

Selwyn BJ. The epidemiology of acute respiratory infection in young children: comparison of findings from several developing countries. Rev Infect Dis 1990;12:Suppl 8:S870-S888.

Shakur MS, Malek MA, Bano N, Islam K. Zinc status in well nourished Bangladeshi children suffering from acute lower respiratory infection. Indian J Pediatr 2004;41:478-81.

Shalit I, Dagan R, Engelhard D, et al. Cefuroxime efficacy in pneumonia: sequential short course i.v./oral suspension therapy. Isr J Med Sci 1994;30:684-9.

Shann F, Barker J, Poore P. Clinical signs that predict death in children with severe pneumonia. Pediatr Infect Dis J 1989;8:852-5.

Shimeles D, Lulseged S. Clinical profile and pattern of infection in Ethiopian children with severe protein-energy malnutrition. East African Medical Journal 1994;71:749-67.

Singhi S, Dhawan A. Frequency and significance of electrolyte abnormalities in pneumonia. Indian Pediatr 1992;29:735-40.

Stapleton T. Chest physiotherapy in primary pneumonia. BMJ 1985;291:143.

Steinhoff M, Black R. Childhood pneumonia: we must move forward. Lancet 2007;369:1409-10.

Subhi R, Adamson M, Campbell H, Weber M, Smith K, Duke T, et al. The prevalence of hypoxaemia among ill children in developing countries: a systematic review. Lancet Infect Dis 2009;9:219-27.

Suskind D, Murthy KK, Suskind RM. The malnourished child: an overview. *In*: Suskind RM, Lewinter- Suskind L, editors. The malnourished child. New York, NY: Vevey/Raven Press, 1990:1-22.

Swingler GH, Hussey GD, Zwarenstein M. Randomised controlled trial of clinical outcome after chest radiograph in ambulatory acute lower respiratory infection in children. Lancet 1998;351:404-8.

Swingler GH. Radiologic differentiation between bacterial and viral lower respiratory infection in children: a systematic literature review. Clin Pediatr 2000;39:627-33.

Swingler GH. Observer variation in chest radiography of acute lower respiratory infections in children: a systematic review. BMC Medical Imaging 2001;1:1.

Toikka P, Irjala K, Juven T, et al. Serum procalcitonin, C-reactive protein and interleukin-6 for distinguishing bacterial and viral pneumonia in children. Pediatr Infect Dis J 2000;19:598-602.

UN General Assembly. United Nations Millennium Declaration. New York: United Nations, 2000. http://www.un.org/millennium/declaration/ares552e.pdf (accessed March 2, 2009).

UNICEF & World Health Organization. Pneumonia: the forgotten killer of children. New York: UNICEF/WHO, 2006

Wafula EM, Ngamau DW, Onyango FE, Mirza NM, Njeru EK. X-ray diagnosable pneumonia in children with severe malnutrition at Kenyatta National Hospital. East African Medical Journal 1998;75:567-71.

Walley J, Lawn J, Tinker A, et al. Primary health care: making Alma-Ata a reality. Lancet 2008;372:1001-7.

Wallis C, Prasad A. Who needs chest physiotherapy? Moving from anecdote to evidence. Arch Dis Child 1999;80:393-7.

Wang EFL, Law BJ, Stephens D, PICNIC. Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) study of morbidity and mortality risk factors with RSV disease. J Pediatr 1995;126:212-9.

Wardlaw TM, Johansson EW, Hodge M, WHO, UNICEF. Pneumonia: the forgotten killer of children. Geneva: World Health Organization, 2006.

Weber MW, Usen S, Palmer A, Jaffar S, Mulholland EK. Predictors of hypoxaemia in hospital admissions with acute lower respiratory tract infection in a developing country. Arch Dis Child 1997;76:310-4.

Weber MW, Mulholland EK. Pulse oximetry in developing countries. Lancet 1998;351:1589.

Williams BG, Gouws E, Boschi-Pinto C, Bryce J, Dye C. Estimates of world-wide distribution of child deaths from acute respiratory infections. Lancet Infect Dis 2002;2:25-32.

World Health Organization. A programme for controlling acute respiratory infections in children: memorandum from a WHO meeting. Bull World Health Organ 1984; 62:47-58.

World Health Organization. Acute respiratory infections in children: case management in small hospitals in developing countries. A manual for doctors and other senior health workers. WHO/ARI/ 90.5. Geneva: WHO, 1990.

World Health Organization. Management of the young child with an acute respiratory infection. Programme for control of acute respiratory infections. Geneva: WHO, 1991.

World Health Organization. Technical basis for the WHO recommendations on the management of pneumonia in children at first-level health facilities (WHO/ARI/91.20). Geneva: WHO, 1991.

World Health Organization. Life in the 21st century. A vision for all. Geneva: WHO, 1998:66.

World Health Organization. Management of the child with a serious infection or severe malnutrition Guidelines for care at the first-referral level in developing countries (WHO/FCH/CAH/00.1). Geneva: WHO, 2000.

World Health Organization. WHO Pocket book of hospital care for children: Guidelines for the management of common illness with limited resources. Geneva: WHO, 2005.

World Health Organization. The clinical use of oxygen in hospitals with limited resources. Guidelines for health-care workers, hospital engineers and managers. Editor: Duke T; Geneva: WHO, 2009.

Zar HJ, Jeena P, Argent A, Gie R, Madhi SA. Diagnosis and management of community-acquired pneumonia in childhood- South African Thoracic Society Guidelines. S Afr Med J 2005;95:977-90.

5

Chronic kidney disease

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1. Introduction

Chronic kidney disease (CKD) is increasingly recognized as a major public health problem. CKD is often under-diagnosed and under-treated because the disease tend to be latent at onset and progress slowly. High blood pressure, diabetes and primary or secondary glomerulonephritis are the main causes of CKD. Today, various diabetic and non-diabetic glomerulopathies form the main contingent of renal replacement therapy (RRT) patients. The above named diseases, therefore, present a major problem encountered in the practice of nephrology. CKD affects many more people than we would even imagine: 1 out of 10 adults in the world have some form of kidney damage. Therefore, early detection and prevention the progression of people with CKD who are also at very high cardiovascular risk, is extremly important challenge and goal especially for all internal medicine practitioners.

CKD represents a progressive, irreversible decline in glomerular filtration rate. Progressive renal function loss is a common phenomenon in renal failure irrespectively of the underlying cause of the kidney disease (Brenner and Anderson 1992; Ots, Pechter et al. 2000). The kidney is able to adapt to damage by increasing the filtration rate in the remaining normal nephrons, a process called adaptive hyperfiltration. As a result, the patient with mild renal insufficiency often has a normal or near-normal serum creatinine concentration. Adaptive hyperfiltration, although initially beneficial, appears to result in long-term damage to the glomeruli of the remaining nephrons, which is manifest by proteinuria and progressive renal insufficiency. This process appears to be responsible for the development of renal failure among those in whom the original illness is either inactive or cured (Post and Rose 2007). Most chronic nephropathies unfortunately lack a specific treatment and progress relentlessly to end stage renal disease. The therapy for the modulation of the renal disease progression has been improved lately because several new antihypertensive drugs which block renin–angiotensin system (RAS) have been introduced to clinical practice, e.g. angiotensin converting enzyme inhibitors (ACEI) (Rubin, Antonaccio et al. 1978) and angiotensin II receptor antagonists (AT_1RA). ACEI proved its effectiveness in the treatment of essential hypertension and congestive heart failure. Later, studies on experimental (Anderson, Meyer et al. 1985) and human diabetic (Lewis, Hunsicker et al. 1993; Brenner, Cooper et al. 2001) and non-diabetic (Maschio, Alberti et al. 1996) renal diseases revealed that the progression of the renal disease can be slowed by RAS blocking treatment that modulates the hemodynamic and non-hemodynamic factors contributing to

the progression. RAS blocking agents have been shown to be renoprotective and, therefore, prescribed not only for antihypertensive but also for renoprotective purposes in diabetic nephropathy and in other chronic glomerular diseases. The cost of the advanced renal failure and renal replacement therapy is enormous. Therefore, early diagnosis and optimal management of CKD as well as premature atherosclerosis affords many challenges for internal medicine practitioners to help to maintain health and life quality among the population at risk.

2. Epidemiology of CKD

There is a rising incidence and prevalence of kidney failure and the worldwide epidemic of CKD shows no signs of abating in the near future. The exact reasons for the growth of the end-stage renal disease are unknown. Changes in the demographics of the population, differences in disease burden among different racial groups and under-recognition of earlier stages and of risk factors for CKD may partially explain this growth. Recent trends show that the rate of increase of new cases of both diabetic and all-cause end-stage renal disease (ESRD) has progressively levelled off in many countries. It is therefore currently impossible to predict the long-term trend of RRT in Europe (Zoccali, Kramer et al.). Zocalli et al have recently acknowledged that in the large, diachronic scenario of systemic epidemiology, CKD is a component of a new epidemic of diseases that, over the twentieth century, replaced malnutrition and infection as leading causes of mortality in the population (Zoccali, Kramer et al.). Neoplasia, cardiovascular and respiratory diseases and diabetes are ascending the priority rank in the global-health agenda. These diseases reduce life expectancy and engender disability in all population strata including the poorest segment of the population, a stratum still considered to be mainly hit by infectious diseases (Zoccali, Kramer et al.).
The ERA-EDTA Registry (http://www.era-edta-reg.org) collects individual and aggregated data from national and/or regional renal registries in Europe and countries bordering the Mediterranean Sea. The individual patient data are used for epidemiological analysis to calculate incidence, prevalence and patient survival. These are published in the Registry annual reports together with aggregated incidence and prevalence data that are received from other European countries.
Diabetes is one of the commonest causes of CKD beside hypertension and glomerulonephritis in many countries (Locatelli, D'Amico et al. 2001; Moeller, Gioberge et al. 2002; Jager and van Dijk 2007). The major groups of diseases leading to ESRD are diabetic nephropathy, hypertension, glomerulonephritis, chronic pyelonephritis and polycystic kidney disease. In different countries the proportions of these diseases as a cause of renal failure vary: e.g. prevalent patients of diabetic nephropathy form from RRT patients in Italy 12%, in Estonia 22%, in Finland and Poland 24%, in Germany 23%, in England 12%, in Japan 30%, and in USA 37%. Very few of the causes of CKD are completely curable. Glomerulonephritis form 22-24% from prevalent renal replacement therapy (RRT) patients in Estonia, Germany, Poland or Finland but only 11-12% in France, Italy or England.

The use of RRT varies in different countries. The prevalence of RRT patients/million inhabitants 2005 was very different worldwide: in Estonia 394, in Finland 675, in Sweden 774, in Germany 1057, in Spain 869, in England 671 or in USA 1590 .
It has been shown that CKD affects men more often than women. For example, according to the Finnish Registry for Kidney Diseases the prevalence of RRT in men was 898 and in

women 553/million inhabitants in 2006. Since 1996, the prevalence of RRT has increased faster among men (63%) than among women (44%). The prevalence among the elderly is growing fast: in the age group 75+ years, the prevalence of RRT has increased by almost 250% during the past ten years and 70% during the past five years. In the younger age groups, the prevalence has increased 10–61% in ten years and 4–14% in five years.

3. Progression of CKD

Several immunologic as well as non-immunologic mechanisms are related to the progression of kidney diseases (Klahr, Schreiner et al. 1988; Remuzzi, Ruggenenti et al. 1997). The nature of the progressive renal damage with various etiologies includes well-known factors where hemodynamics (Hostetter, Olson et al. 1981), participation of RAS and progressive proteinuria (Williams and Coles 1994)play central roles (Remuzzi, Ruggenenti et al. 1997).
In chronic renal failure, after the loss of a critical number of nephrons, the remaining nephrons undergo compensatory functional and structural adaptations. During this process, the surviving nephrons lose the capacity to autoregulate glomerular flows and pressures and become vulnerable to the effects of systemic hypertension, which is readily accompanied by glomerular hypertension, hyperfiltration and hypertrophy (Hostetter, Olson et al. 1981). Angiotensin II is important in mediating glomerular hemodynamics and contributes to the rise of intraglomerular and systemic blood pressure. In essential and secondary hypertensive states, at a certain stage, an increase in intraglomerular capillary pressure plays a role in the acceleration of the loss in renal function. Hypertension is a risk factor for the development of atherosclerosis (Ross 1986), for all-cause mortality (O'Donnell, Ridker et al. 1997), but also of glomerulosclerosis in various etiologies (Klag, Whelton et al. 1996). These two processes share several common mechanism (Diamond 1991), e.g. hormonal, cellular and molecular events although these have not been entirely elucidated. Central to the pathogenesis of atherosclerosis is the interaction of blood cells and endothelial cells with subsequent proliferation of smooth muscle cells and enhanced production of collagen. The mechanisms that appear to be responsible for this increased proliferative response are growth factors, cytokines, and local alterations in the extracellular matrix proteins. There is increasing evidence that atherosclerosis should be viewed fundamentally as an inflammatory disease (Raines and Ross 1997) where risk factors such as hypertension, humoral factors (Raij 1991), hyperlipidemia (Devaraj and Jialal 1996), lipid deposition in vessels and later development of atherosclerotic lesions play central roles in the progression. As in the case of atherosclerosis, there is an inflammatory content involved in kidney fibrosis in human (Noronha, Niemir et al. 1995) or experimental glomerulonephritides (Lloyd, Minto et al. 1997), and even in classical glomerulosclerotic models previously thought to be non-inflammatory, e.g. remnant kidney (Schiller and Moran 1997). Infiltration of mononuclear leucocytes in glomerular and tubulointerstitial areas, upregulation of proinflammatory cytokines and growth factors after the initiation of the disease play important roles in the progression (Schiller and Moran 1997). The glomerulosclerosis process includes mesangial expansion with mesangial cell proliferation, mesangial foam cell accumulation, tissue necrosis, and eventual sclerosis. Substances that interfere with the interaction between the different cell types, such as endothelial cells, macrophages, and platelets, and with the proliferative responses of both vascular and mesangial cells may be of therapeutic value in both diseases.

Data about the upregulation of various proinflammatory cytokines are similarly available for other non-inflammatory renal diseases such as diabetic nephropathy and certainly for human nephropathies (Niemir, Stein et al. 1995; Kato, Luyckx et al. 1999). Wagner et al. provided technical evidence that using PCR may give a possibility in the future to analyze expressions of genes which may contribute to renal damage in human biopsies (Wagner, Drab et al. 1994). Knowing key molecules, which play a pathophysiological role or serve as markers for the progression of renal disease may allow more precise staging of the disease and better indicate therapeutic needs in particular diseases. Cytokines have also been demonstrated in other biological samples, e.g. urine. The results of Noh et al. (Noh, Wiggins et al. 1993) suggest that measurements of urinary activity of transforming growth factor beta (TGF-β) at certain critical stages of the disease could be useful in predicting the progression to end-stage renal disease with fibrosis. Therefore, a urine test for the detection of particular growth factors might serve as a helpful non-invasive adjunct in monitoring the response to therapy. Much interest has been paid to TGF-β because the key action of this growth factor is the induction of the extracellular matrix protein production. Specific matrix proteins are known to be induced by TGF-β, which were increased in experimental kidney disease rat glomeruli. For instance, Yamamoto et al. has shown the correlation of TGF-β (Yamamoto, Noble et al. 1994) with the accumulation of extracellular matrix proteins in the glomerulonephritis model and the treatment with the inhibitor of TGF-β prevents scarring of the kidney. Yamamoto et al. were able to show that in the rats given a second antibody injection of an antibody reactive with glomerular mesangial cells, 1 week later, the glomerular expression of TGF-β-1 mRNA and TGF-β-1 protein remained elevated for 18 weeks. It was associated with a large infiltration of mononuclear cells with staining features of fibroblastic/myofibroblastic cells, strongly expressing TGF-β in the tubulointerstitium of the kidney (Yamamoto, Noble et al. 1994). A single injection of antibody resulted only in the transient upregulation of TGF-β. These data suggest that sustained TGF-β expression contributes to the development of progressive kidney fibrosis. TGF-β, monocyte chemoattractant protein-1 (MCP-1) mRNA and protein expression as well as macrophage infiltration dynamics have been investigated in experimental diabetic nephropathy (Kato, Luyckx et al. 1999). In these studies sustained TGF-β and MCP-1 overexpression was also observed. This particular gene expression was closely associated with the extent of macrophage infiltration and proteinuria (Kato, Luyckx et al. 1999).

Much attention has recently been paid to the importance of persistent proteinuria, an independent risk factor of renal disease progression (Klahr, Schreiner et al. 1988; Williams and Coles 1994). Proteins filtered through the glomerular capillary in excessive amount activate proximal tubular cells to upregulate chemokines mainly via activation of NF-kappaB-dependent pathway. The association between proteinuria and interstitial accumulation of inflammatory cells via activation of transcription factors and overexpression of chemokines has been established both experimentally and in human proteinuric nephropathies (Zoja, Garcia et al. 2009). Biochemical events associated with tubular cell activation in response to protein stress include upregulation of inflammatory and vasoactive genes such as MCP-1 and endothelins. These molecules are associated with a tubulointerstitial inflammatory reaction that in most forms of glomerulonephritis consistently proceeds renal scarring. Adequate early antiproteinuric therapy may arrest the progression of the renal disease or even lead to the regression of the disease. Also, disturbances in lipid metabolism, participation of cellular and molecular factors and

subsequent accumulation of extracellular matrix components with the development of kidney fibrosis are closely related to the progression (Floege, Burns et al. 1992; Remuzzi, Ruggenenti et al. 1997). Clarification of the mechanisms underlying progression of proteinuric nephropathies received significant input from the generation of transgenic and knockout animals and from novel approaches to block mediators of injury. Recent findings have shown that gene targeting in rodents identified podocyte loss as central event in the development of glomerulosclerosis. The trigger is dysfunction or absence of podocyte molecules that stabilize the slit diaphragm or anchor foot processes to the basement membrane. Sustained injury of the glomerular barrier to proteins is transmitted to the tubulointerstitial compartment leading to inflammation and fibrosis. Blocking NF-kappaB activity and chemokine signals in the kidney effectively interrupts such process. Growth factors produced by tubular cells and inflammatory cells contribute to interstitial fibrogenesis via myofibroblast activation. This knowledge will provide basis for novel interventions to protect the podocyte in chronic progressive glomerulopathies and to halt renal scarring and loss of function (Zoja, Abbate et al. 2006).

4. CKD progression prevention strategies

Various therapies have been studied which may protect kidneys against progressive injury including at least two experimentally and clinically confirmed strategies: a reduction in protein intake (Brenner, Meyer et al. 1982) or a lowering in blood pressure (Anderson, Meyer et al. 1985). Systemic hypertension complicates experimental glomerulosclerosis and the clinical course of patients with chronic renal failure, and, if inadequately controlled, may hasten the deterioration of renal function (Klag, Whelton et al. 1996). In diabetic and non-diabetic patients with proteinuria controlling blood pressure with RAS blocking agents slows significantly the rate of the decline of the glomerular filtration rate (GFR).

Other cardiovascular risk factors also play important roles in the progressive renal disease. Beside hypertension, smoking (Orth 2000), obesity or hyperlipidemia has not been intensively investigated in the early stages of renal disease. Usually hyperlipidemia is thought to be associated more with ongoing atherosclerotic process. Nevertheless, experimental studies have been shown that lipid abnormalities themselves can influence the progression of renal disease and lipid oxidation is increased in animal and human glomerular disease. Increased nephron oxygen radical generation leads to renal tissue lipid peroxidation. On the other hand, antioxidative therapy has been shown to be effective on antioxidative status in experimental diabetes and in human hypertension. Antilipemic therapy may also be beneficial in ameliorating renal disease progression.

It has been shown that the inhibition of TGF-β leads to the protection of scarring in experimental kidney diseass. The modulation of the human renal disease process with inhibiting directly particular cytokine upregulation or even prevent fibrotic events, awaits future confirmation studies.

The concept of nephro- or renoprotection as a definitive proof of ACEI for superior efficacy on systemic and intraglomerular pressure, proteinuria and renal disease progression was not defined until the results of clinical trials became available. It is proposed that in treating hypertension we should aim at reducing systemic blood pressure together with an attempt to reduce intraglomerular pressure using the agents that act predominantly on post-glomerular resistance in order to have renal protection. Both RAS blocking drugs, ACEI and

AT_1RA have achieved these parameters, and the renoprotective effect includes their impact on the hemodynamics, on the reduction of the filtration of plasma proteins, on the preservation of kidney function as well as the structure. Therefore, these agents have already been accepted in the treatment of diabetic and non-diabetic nephropathies in order to arrest and/or prevent renal damage.

There is convincing evidence that beside diuretics, adrenoblocking agents, beta-blockers, calcium channel blockers and other antihypertensive medications, administration of RAS blocking agents promise better control of glomerular hypertension and long-term outcome of kidney preservation than other agents. Moreover, experimental as well as clinical data suggest that ACEI reduce proteinuria and retard the progression of the renal disease to a greater degree than can be explained by their blood pressure lowering effects alone. Effective blockade of RAS with ACEI preventing sustained elevation of systemic blood pressure, lowering intracapillary pressure, lowering proteinuria modulating hyperlipidemia and inhibition of renal growth have been shown to reduce kidney injury and protect the kidney even further during the ongoing disease process. The ACEI, by decreasing angiotensin II generation, induce glomerular efferent arteriolar dilation as well as mesangial relaxation. These combined effects explain a reduced glomerular capillary pressure. The fall in filtration pressure contributes to the antiproteinuric effect and also to the long-term renoprotection.

Glomerulosclerosis and interstitial fibrosis that accompany experimental and human glomerulopathies can also be ameliorated by ACEI or AT_1RA administration. Proteinuria itself is involved in the final common pathway of the progressive renal function loss. It has been hypothesized that the presence of large quantities of protein within the tubules may have a damaging effect on the tubular cells and interstitium. This is particularly relevant since attention has recently been focused on a well-known but an ignored fact that the progression of renal disease best correlates with the extent of interstitial damage and not with glomerulosclerosis per se. Remuzzi et al. have summarized the evidence that the process of reabsorption of filtered proteins activates the proximal tubular epithelium (Remuzzi, Ruggenenti et al. 1997).

Most experimental studies that compared the effects of ACEI and AT_1RA have shown a striking similarity of actions between these classes of drugs. Similarly, the effect of ACEI, AT_1RA has also been shown to lower the systemic and intraglomerular pressure as well as proteinuria and morphological lesions. Combination therapy with ACEI and AT_1RA is similar to those of enalapril or losartan alone and are related to the magnitude of their systemic antihypertensive effects (Ots, Mackenzie et al. 1998). These results indicate that both ACEI and AT_1RA can lower blood pressure at least as effectively as ACE inhibitors and also be renoprotective. In diabetic and non-diabetic patients with proteinuria controlling blood pressure with RAS blocking agents slows significantly the rate of the decline of the glomerular filtration rate (GFR) (Mogensen, Keane et al. 1995). Moreover, the treatment has good effect also for cardiovascular outcome of patients with CKD(Brenner, Cooper et al. 2001). In conclusion, many recent experimental and clinical studies have shown that besides the systemic blood pressure lowering effect, RAS blocking agents provide renal protective effects via direct, hemodynamic, and indirect, non-hemodynamic, pathways: (1) lowering intraglomerular capillary hydraulic pressure, and increasing the glomerular ultrafiltration coefficient; (2) lowering proteinuria; (3) lowering hyperlipidemia; (4) diminishing kidney growth; (5) diminishing infiltration of macrophages; (6) downregulation of proinflammatory cytokines. Therefore, RAS blocking agents are widely prescribed not only for antihypertensive but also for renoprotective purposes in diabetic and

non-diabetic nephropathies. In order to slow to the greatest extent progression of renal disease, the ideal therapeutic approach for patients with proteinuric nephropathies should be a multimodal strategy including dual RAS blockade, antialdosterone therapy, lipid-lowering agents, smoking cessation, and tight glucose control for diabetes.

5. Management of CKD patients

Clinical evaluation for CKD should include elucidation of the cause of disease. Also, for determining the stage and specific characteristics of the underlying disease follow-up of patients and thorough diagnostic work-up is needed. However, the cause of the disease cannot be ascertained in all cases because renal function declines also normally with age and the exact level of decline at a given age that should be considered pathological is not known. Cross-sectional studies report a slow decline in GFR after the fourth decade of life ~ 0.75 mL/min./1.73 m^2/year. These changes proceed slowly but in the presence of other diseases such as diabetes, hypertension and heart disease, the kidney becomes vulnerable to failure (Pannu and Halloran 2001). The KD:IGO (Kidney Disease: Improving Global Outcomes) statement considers GFR less than 60 mL/minute pathological at all ages. CKD is classified according to severity, diagnosis, treatment and prognosis. Five-stage classification is based on structural and functional criteria regardless of the cause and accounting for dialysis and transplantation (Gregorio, Obrador et al. 2007).

The National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) workgroup has defined CKD as the following (2002), which have been accepted internationally with some clarifications (Levey, Eckardt et al. 2005; Gregorio, Obrador et al. 2007):

1 The presence of markers of kidney damage for 3 months, as defined by structural or functional abnormalities of the kidney with or without decreased glomerular filtration rate (GFR), that can lead to decreased GFR, manifest by either pathological abnormalities or other markers of kidney damage, including abnormalities in the composition of blood or urine, or abnormalities in imaging tests

2 Or the presence of GFR<60 mL/min./1.73 m^2 for 3 months, with or without other signs of kidney damage as described above.

Based upon representative samples of the United States population (2002), the studies have estimated the prevalence of CKD in the general population through measurement of markers of kidney damage, such as elevated serum creatinine concentration, decreased predicted GFR and presence of albuminuria.

According to the Kidney Disease: Improving Global Outcomes (KD:IGO) position statement the use of the term "disease" in CKD is consistent with:

1) the need for action to improve outcomes through prevention, detection, evaluation and treatment;
2) providing a message for public, physician and patient education programs;
3) common usage; and
4) its use in other conditions defined by findings and laboratory tests, such as hypertension, diabetes and hyperlipidaemia (Levey, Eckardt et al. 2005).

CKD is classified according to severity, diagnosis, treatment and prognosis (Levey, Eckardt et al. 2005). Five-stage classification is based on structural and functional criteria regardless of the cause and accounting for dialysis and transplantation (Table 1).

Stage	Description	GFR (mL/min. per 1.73 m^2)	Related terms
1	Kidney damage with normal or ↑ GFR	≥ 90	Albuminuria Proteinuria Haematuria
2	Kidney damage with mild ↓ GFR	60–89	Albuminuria Proteinuria Haematuria
3	Moderate ↓ GFR	30–59	Chronic renal insufficiency Early renal insufficiency
4	Severe ↓ GFR	15–29	Chronic renal insufficiency Late renal insufficiency Pre-ESRD
5	Kidney failure	<15	Renal failure Uraemia End-stage renal disease

Table 1. Classification of chronic kidney disease.

There is an overwhelming consensus that screening for CKD should include high-risk groups. Early detection of diabetes and hypertension as the most important reasons for CKD and their appropriate treatment is a method of avoiding or postponing complications, incl. chronic kidney failure. Screening of hypertension by measurement of blood pressure at office visits has found support in many guidelines. In clinical studies the extent of proteinuria correlates with the faster decline of glomerular filtration rate in patients with chronic renal diseases. Therefore, strict monitoring of proteinuria helps in the optimal management of patients.

Risk groups of chronic kidney disease are the follows:

- Patients with a family history of diabetes, hypertension
- Diabetics
- Hypertensive patients
- Recurrent urinary tract infections
- Urinary obstruction
- Patients with systemic diseases that affect kidneys
- Patients with past or family history of cardiovascular disease

The most widely used methods for screening for kidney disease are: 1) an analysis of a random urine sample for albuminuria and, 2) a serum creatinine measurement to calculate an estimated GFR, which is an indication of functioning kidney mass. It is recommendable to use both of these methods as significant kidney disease can present with diminished GFR or proteinuria, or both (Garg, Kiberd et al. 2002). Detecting and quantitation of proteinuria are essential to the diagnosis and treatment of CKD. Albumin, the predominant protein excreted by the kidney in most types of renal diseases, can be detected by urine dipstick testing. The protein-creatinine ratio in an early-morning random urine sample correlates

well with 24-hour urine protein excretion and is much easier to obtain (2002). Albuminuria often heralds the onset of diabetic nephropathy, thus this sample is therefore recommended for all patients at risk for kidney disease. The quantitative determination of protein in the urine in the laboratory is more economical and more correct, than the use of microalbuminuria dipsticks and should be the recommended method to detect proteinuria. The term "albuminuria" should be substituted for the terms "microalbuminuria" and "macroalbuminuria." These terms are commonly used but should be avoided because they are misleading (2005). Increased urinary excretion of albumin is the earliest manifestation of CKD due to diabetes, other glomerular diseases and hypertensive nephrosclerosis. Also, albuminuria may also accompany tubulointerstitial diseases, polycystic kidney disease and kidney disease in transplant recipients.

Significant kidney dysfunction may be present despite a normal serum creatinine level. An estimated GFR based on serum creatinine level correlates better with direct measures of the GFR and detects more cases of CKD than does the serum creatinine level alone. Clinically useful GFR estimates are calculated from the measured serum creatinine level after adjustments for age, sex and race (Cockcroft and Gault 1976; Levey, Bosch et al. 1999). The two most commonly used formulas for GFR estimation are the MDRD (Modification of Diet in Renal Disease) study equation and the Cockcroft–Gault equation (Table 2). Validation studies in middle-aged patients with CKD showed the MDRD study equation to be more accurate (Levey, Bosch et al. 1999). However, the MDRD study equation was found to systematically underestimate the GFR in patients without CKD. It is important to realise that the methodology used for determination of serum creatinine is of great importance in the interpretation of the results obtained with the MDRD formula and that in fact, only the IDMS-corrected serum creatinine can be used (Van Biesen, Vanholder et al. 2006). It should be kept in mind that these formulas do not result in correct GFRs when used in persons with abnormal body composition: the obese, patients with oedema, pregnancy, states of cachexia or amputees. In most situations of family doctors and as long as kidney function is stable, a calculated GFR can replace measurement of a 24-hour urine collection for creatinine clearance, that is still required in pregnant women, patients with extremes of age and weight, patients with malnutrition, patients with musculoskeletal diseases, paraplegia or quadriplegia and patients with a vegetarian diet or rapidly changing kidney function (Snyder and Pendergraph 2005). Also, creatinine clearance is preferred in predialysis and transplant patients.

Abbreviated MDRD study equation (Levey, Bosch et al. 1999)	GFR (mL per minute per 1.73 m^2) = 186 x $(S_{Cr})^{-1.154}$ x $(age)^{-0.203}$ x (0.742, if female) x (1.210, if black)
IDMS traceable MDRD formula (Van Biesen, Vanholder et al. 2006)	GFR (mL per minute per 1.73 m^2) = 175 x standardised $S(_{Cr})^{-1.154}$ x $(age)^{-0.203}$ x (0.742, if female) x (1.212, if black)
Cockcroft–Gault equation (Cockcroft and Gault 1976)	GFR (mL/min.) = $\frac{(140 - age) \times weight}{0.81 \times S_{Cr}}$ x (0.85, if female)

GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease;
S_{Cr} = serum creatinine concentration (µmol/L);

Table 2. Estimated glomerular filtration rate mathematical formulas.

6. Conclusion

Glomerular cellular changes such as platelet infiltration, mesangial cell proliferation, increased expression of proinflammatory cytokines and growth factors, as well as tubulointerstitial changes that occur early in the development of the remnant kidney progression and other models of chronic renal insufficiency, were linked to the later development of kidney fibrosis. Nowadays, there is evidence that RAS inhibition, besides the effects on glomerular hemodynamics, influence other pathogenic mechanisms of progressive renal insufficiency, e.g. hypertrophy, proteinuria, hyperlipidemia, kidney growth, infiltration of macrophages, expression of proinflammatory cytokines, etc. As previously shown in animal and clinical studies, RAS blocking agents effectively affect those pathogenetical processes of the progression of renal disease which are not unique but are similar for certain nephropathy, and, therefore, deserve to be referred to as renoprotection drugs. This is a new concept that came together with the introduction of ACEI in the mid-1980s in conjunction with their effect on glomerular hemodynamics in experimental settings and, later, in clinical works.

In human chronic renal diseases, the RAS blocking therapy can arrest the decline of the GFR in diabetics and non-diabetics. When to start the treatment and which dose to choose? The optimal dose has not been determined yet. In experimental studies, optimal dosing and timing the treatment is easy to determine. In the cases of human chronic renal diseases where the onset of the disease is often insidious and at the time of renal biopsy the disease is often already advanced, uncertainty still persists with respect to the relative indications for early RAS blockade, especially if the patient does not have hypertension. A better understanding of the pathomechanisms of renal disease progression may allow us to develop more precise laboratory tests for early diagnosis of various nephropathies. Thus, usage of protein and gene expression techniques in renal biopsies or new serum or urine tests may afford, in future probably, more accurate detection of early renal alterations. Today we have mainly descriptive data about the relevance of these factors in human chronic renal diseases and much work waits before molecular diagnosis becomes available. Knowledge about the pathogenesis of renal disease progression, the use of more precise methods for evaluating renal disease evolution and the determination of the disease stage may lead to better control of the progression of renal disease in future and, as a result, reduce the number of patients reaching end-stage renal failure.

7. References

"ERA-EDTA registry annual report." http://www.era-edta-reg.org/index.jsp?p=annrep.

"Finnish Registry for Kidney Diseases." http://www.musili.fi/fin/munuaistautirekisteri/finnish_registry_for_kidney_diseases/.

"UK Chronic Kidney Disease Guideline." http://www.renal.org/eGFR/eguide.html.

"UK Renal Registry." http://www.renalreg.com/.

"United States Renal Data System." http//www.usrds.org.

(2002). "K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification." Am J Kidney Dis **39**(2 Suppl 1): S1-266.

(2005). "KD:IGO Position Statement." http://www.nature.com/isn/education/guidelines/isn/full/ed_051027_3.html.

Anderson, S., T. W. Meyer, et al. (1985). "Control of glomerular hypertension limits glomerular injury in rats with reduced renal mass." J Clin Invest **76**(2): 612-9.

Brenner, B. M. and S. Anderson (1992). "The interrelationships among filtration surface area, blood pressure, and chronic renal disease." J Cardiovasc Pharmacol **19 Suppl 6**: S1-7.

Brenner, B. M., M. E. Cooper, et al. (2001). "Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy." N Engl J Med **345**(12): 861-9.

Brenner, B. M., T. W. Meyer, et al. (1982). "Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease." N Engl J Med **307**(11): 652-9.

Cockcroft, D. W. and M. H. Gault (1976). "Prediction of creatinine clearance from serum creatinine." Nephron **16**(1): 31-41.

Devaraj, S. and I. Jialal (1996). "Oxidized low-density lipoprotein and atherosclerosis." Int J Clin Lab Res **26**(3): 178-84.

Diamond, J. R. (1991). "Analogous pathobiologic mechanisms in glomerulosclerosis and atherosclerosis." Kidney Int Suppl **31**: S29-34.

Floege, J., M. W. Burns, et al. (1992). "Glomerular cell proliferation and PDGF expression precede glomerulosclerosis in the remnant kidney model." Kidney Int **41**(2): 297-309.

Garg, A. X., B. A. Kiberd, et al. (2002). "Albuminuria and renal insufficiency prevalence guides population screening: results from the NHANES III." Kidney Int **61**(6): 2165-75.

Gregorio, T., B. Obrador, et al. (2007). "Epidemiology of chronic kidney disease and screening recommendations. 2007." UpToDate **15.3**.

Hostetter, T. H., J. L. Olson, et al. (1981). "Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation." Am J Physiol **241**(1): F85-93.

Jager, K. J. and P. C. van Dijk (2007). "Has the rise in the incidence of renal replacement therapy in developed countries come to an end?" Nephrol Dial Transplant **22**(3): 678-80.

Kato, S., V. A. Luyckx, et al. (1999). "Renin-angiotensin blockade lowers MCP-1 expression in diabetic rats." Kidney Int **56**(3): 1037-48.

Klag, M. J., P. K. Whelton, et al. (1996). "Blood pressure and end-stage renal disease in men." N Engl J Med **334**(1): 13-8.

Klahr, S., G. Schreiner, et al. (1988). "The progression of renal disease." N Engl J Med **318**(25): 1657-66.

Levey, A. S., J. P. Bosch, et al. (1999). "A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group." Ann Intern Med **130**(6): 461-70.

Levey, A. S., K. U. Eckardt, et al. (2005). "Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO)." Kidney Int **67**(6): 2089-100.

Lewis, E. J., L. G. Hunsicker, et al. (1993). "The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group." N Engl J Med **329**(20): 1456-62.

Lloyd, C. M., A. W. Minto, et al. (1997). "RANTES and monocyte chemoattractant protein-1 (MCP-1) play an important role in the inflammatory phase of crescentic nephritis, but only MCP-1 is involved in crescent formation and interstitial fibrosis." J Exp Med **185**(7): 1371-80.

Locatelli, F., M. D'Amico, et al. (2001). "The epidemiology of end-stage renal disease in the Baltic countries: an evolving picture." Nephrol Dial Transplant **16**(7): 1338-42.

Maschio, G., D. Alberti, et al. (1996). "Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group." N Engl J Med **334**(15): 939-45.

Moeller, S., S. Gioberge, et al. (2002). "ESRD patients in 2001: global overview of patients, treatment modalities and development trends." Nephrol Dial Transplant **17**(12): 2071-6.

Mogensen, C. E., W. F. Keane, et al. (1995). "Prevention of diabetic renal disease with special reference to microalbuminuria." Lancet **346**(8982): 1080-1084.

Niemir, Z. I., H. Stein, et al. (1995). "PDGF and TGF-beta contribute to the natural course of human IgA glomerulonephritis." Kidney Int **48**(5): 1530-41.

Noh, J. W., R. Wiggins, et al. (1993). "Urine transforming growth factor-beta activity is related to the degree of scarring in crescentic nephritis in the rabbit." Nephron **63**(1): 73-8.

Noronha, I. L., Z. Niemir, et al. (1995). "Cytokines and growth factors in renal disease." Nephrol Dial Transplant **10**(6): 775-86.

O'Donnell, C. J., P. M. Ridker, et al. (1997). "Hypertension and borderline isolated systolic hypertension increase risks of cardiovascular disease and mortality in male physicians." Circulation **95**(5): 1132-7.

Orth, S. R. (2000). "Smoking--a risk factor for progression of renal disease." Kidney Blood Press Res **23**(3-5): 202-4.

Ots, M., H. S. Mackenzie, et al. (1998). "Effects of combination therapy with enalapril and losartan on the rate of progression of renal injury in rats with 5/6 renal mass ablation." J Am Soc Nephrol **9**(2): 224-30.

Ots, M., U. Pechter, et al. (2000). "Characteristics of progressive renal disease." Clin Chim Acta **297**(1-2): 29-41.

Pannu, N. and P. F. Halloran (2001). " The kidney in aging " Primer in Kidney Diseases 3rd ed.

Post, T. W. and M. D. Rose (2007). "Overview of the management of chronic kidney disease in adults." UpToDate **15.3**.

Raij, L. (1991). "Hypertension, endothelium, and cardiovascular risk factors." Am J Med **90**(2A): 13S-18S.

Raines, E. W. and R. Ross (1997). "Is overamplification of the normal macrophage defensive role critical to lesion development?" Ann N Y Acad Sci **811**: 76-85; discussion 85-7.

Remuzzi, G., P. Ruggenenti, et al. (1997). "Understanding the nature of renal disease progression." Kidney Int **51**(1): 2-15.

Ross, R. (1986). "The pathogenesis of atherosclerosis--an update." N Engl J Med **314**(8): 488-500.

Rubin, B., M. J. Antonaccio, et al. (1978). "Captopril (SQ 14,225) (D-3-mercapto-2-methylpropranoyl-L-proline): a novel orally active inhibitor of angiotensin-converting enzyme and antihypertensive agent." Prog Cardiovasc Dis **21**(3): 183-94.

Schiller, B. and J. Moran (1997). "Focal glomerulosclerosis in the remnant kidney model--an inflammatory disease mediated by cytokines." Nephrol Dial Transplant **12**(3): 430-7.

Snyder, S. and B. Pendergraph (2005). "Detection and evaluation of chronic kidney disease." Am Fam Physician **72**(9): 1723-32.

Zoccali, C., A. Kramer, et al. "Epidemiology of CKD in Europe: an uncertain scenario." Nephrol Dial Transplant **25**(6): 1731-3.

Zoja, C., M. Abbate, et al. (2006). "Progression of chronic kidney disease: insights from animal models." Curr Opin Nephrol Hypertens **15**(3): 250-7.

Zoja, C., P. B. Garcia, et al. (2009). "The role of chemokines in progressive renal disease." Front Biosci **14**: 1815-22.

Wagner, J., M. Drab, et al. (1994). "PCR analysis of human renal biopsies--renin gene regulation in glomerulonephritis." Kidney Int **46**(6): 1542-5.

Van Biesen, W., R. Vanholder, et al. (2006). "The importance of standardization of creatinine in the implementation of guidelines and recommendations for CKD: implications for CKD management programmes." Nephrol Dial Transplant **21**(1): 77-83.

Williams, J. D. and G. A. Coles (1994). "Proteinuria--a direct cause of renal morbidity?" Kidney Int **45**(2): 443-50.

Yamamoto, T., N. A. Noble, et al. (1994). "Sustained expression of TGF-beta 1 underlies development of progressive kidney fibrosis." Kidney Int **45**(3): 916-27.

6

Integrated vehicle health management in the automotive industry

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1. Introduction

The advent of integrated vehicle health management (IVHM) in the auto industry promises to provide significant new capabilities to enhance the overall customer ownership experience with their vehicles. In essence, it provides a means to essentially redefine "reliability" by being able to proactively deal with future problems before they actually inconvenience the customer and, thus, largely mitigate the negative impact of those problems. IVHM provides an important building block upon which these innovative new features can be implemented. In addition, IVHM provides an improved framework to better manage the life cycle maintenance for such vehicles which in turn provides an immediate saving opportunity for all vehicles. Traditional maintenance schedules in automotive use have typically been time or mileage based but this can lead to negative consequences in multiple ways. The maintenance intervals can be too conservative for some operating conditions and therefore potentially waste the owner's time and money as well as wasting valuable natural resources. On the other extreme, under certain operating conditions, the time or mileage based approach may signal a maintenance action too late to avoid a service issue of some kind. By tracking actual usage patterns, we can dynamically adapt the maintenance intervals to more appropriate periods based on the actual needs. This has been shown to result in significant benefits.

2. IVHM in the New Paradigm

IVHM is all about active management of the automotive vehicle's health, as it relates to the performance of key vehicle functions, to meet the customer's need for reliable transportation. It is instructive to consider the broad ramifications of IVHM in the context of the new paradigm the auto industry has entered. This is important because the assumptions and limitations implicit in today's designs will simply no longer apply as this new paradigm takes hold.

In the early days of the auto industry at the start of the twentieth century, the paradigm was truly one of "craft manufacturing." Even though the notion of interchangeable parts had been successfully applied in the gun manufacturing business, the same concept was

considered totally impractical relative to much more complex products such as automobiles. Henry Leland, founder of Cadillac, set out to prove otherwise and won the prestigious Dewar Trophy in 1908[1] with the successful demonstration of interchangeable parts held for the Royal Automobile Club of England (RAC). This second paradigm in turn laid the foundation for the third paradigm later introduced by the other Henry [Ford] who popularized the concept of the assembly line[2] based in part on what he learned from the meat packaging business. The assembly line paradigm dominated the industry for many years until Toyota's Taichi Ohno introduced what has since become known as Lean Manufacturing[3]. He got those ideas in part from the grocery business and its obsession with waste reduction driven by the perishable nature of their product and their very thin profit margins. But, just as lean built upon the assembly line which built upon interchangeable parts, we have now entered what I call the paradigm of "real time optimization."

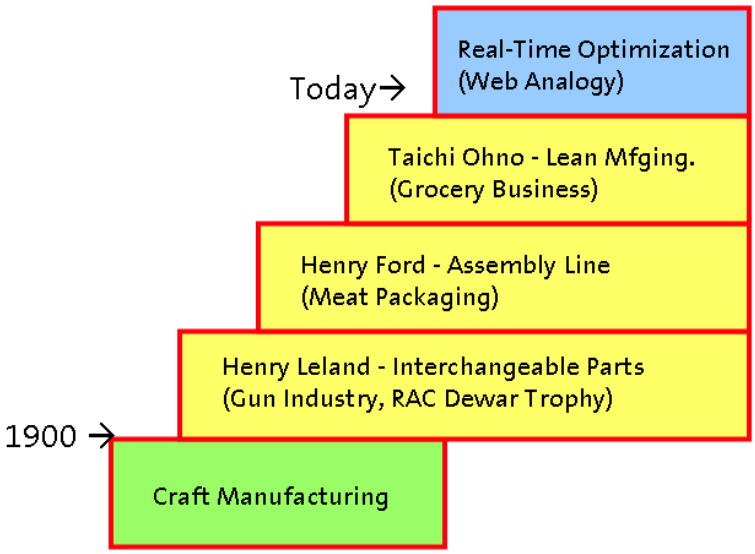

Fig. 1. Automotive Manufacturing Paradigms

The "real time optimization" paradigm draws heavily upon the lessons learned in the creation of the World Wide Web. There were a number of prerequisites before the web could explode into becoming the global phenomena that it represents today. I believe that reaching critical mass in both computational power and communication bandwidth was perhaps even more important than the advent of the browser. In automotive manufacturing today, we now have computers embedded in nearly all key manufacturing equipment such as robots, material handling systems, control systems (PLCs), ordering systems, supply systems, etc. Equally important is that we now have both high speed wired or wireless communications between all these smart machines or functions. Thus, we have begun witnessing a similar kind of explosion of capability in manufacturing as seen previously with the Web.

Just as lean manufacturing was to spill over into all aspects of business operations, so it is the case for the real time optimization paradigm.

> ***This paradigm beyond "lean" is being driven by the availability and exploitation of real-time information across the enterprise to optimize the value chain from the suppliers through manufacturing plants, and into the distribution channel.***

IVHM as we conceive it would not be possible without the real time optimization paradigm. It is precisely the elements of this paradigm which provide a means for knitting together all the engineering and business processes which taken together provide us our vision for IVHM. Modern vehicles already have upwards of 50 microprocessors on board to control the various subsystems of the vehicle. The software codes that deal with engines, transmissions, overall vehicle coordination, etc. already exceed one million lines of code each. The data storage on board to support entertainment and navigation systems typically requires gigabytes of data. This complexity will only continue to grow as the electrification of automobiles goes mainstream in the market and as sophisticated computer controlled safety systems advance[4].

3. Customer Needs & Wants

It is essential to consider customer needs and wants as we prepare to provide fundamentally new services through IVHM technologies. One important analysis of that topic comes from J.D. Power and Associates studies on how customers themselves evaluate the various elements that impact their overall satisfaction. As shown in Figure 2, *Quality and Reliability* is the single biggest factor typically accounting for 38-41% of the overall score. It is not surprising that it is the single most important factor but one should take note that it does not by itself tell the whole story. The next factor is *Vehicle Appeal* at 22-26% of the score – this includes performance, design, comfort, features, etc. *Ownership Costs* represent about 18-20% and includes fuel consumption, insurance and costs of service/repair. Lastly, *Dealer Service Satisfaction* typically accounts for about 16-19% of the score. Clearly, there is no single factor and thus one needs to be mindful of all the areas. IVHM is very interesting as a new automotive concept as it has the potential to positively impact all four elements of customer satisfaction.

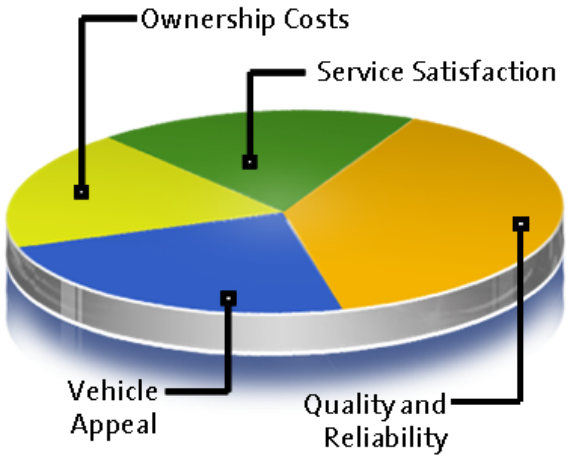

Fig. 2. Elements of Customer Satisfaction

We know from surveys that our customers do understand and appreciate currently available prognostic features such as GM's oil life monitor which is available on most of our products. The remaining useful life of the engine oil is monitored by onboard computers and is calculated based on actual driving conditions. People who drive only short distances with a lot of "stop and go" city driving may need to replace their oil after only 2,500 miles whereas those that tend to do mostly longer distance highway driving may be able to comfortably go 12,000 miles or more before a change. This is perhaps one small example but the point is important. That is, the amount of oil you can potentially save over the entire fleet of vehicles offers a significant societal benefit. In addition, there is a huge collective cost savings which accrues directly to customers by avoiding the expense of unnecessary oil changes and wasted time. The oil life monitor relates to just one of the consumables needed by typical vehicles but, of course, the same approach might apply to the other normal, time-based or mileage-based maintenance schedules. Looking to the future, we believe it is important to go beyond the normal maintenance items and be able to deal proactively with the health of all major systems onboard the vehicle as this specifically is what leads to significantly enhanced reliability as experienced by the customer.

As automotive technology has improved over the years, we have observed a trend of achieving higher and higher levels of quality, reliability and durability (often referred to as QRD). There is little question that this is important to prospective buyers and therefore important to the manufacturers as well. All manufacturers need to keep sharply focused on this need but QRD statistics alone do not tell the whole story. If we can exploit prognosis to predict problems before they negatively impact the customer, we will have essentially created an opportunity to redefine what reliability means from the customer's point of view. That is, if we can detect future problems at a point early enough to allow us to intervene on behalf of the customer and proactively resolve the issue before the customer is inconvenienced, we have essentially achieved this redefinition of reliability.

4. Automotive IVHM

Prognosis advances are creating new opportunities for applying IVHM in the automotive business. It clearly needs to be managed from a life cycle perspective and from a total business point of view as illustrated in Figure 3. Looking at warranty costs alone is too narrow a scope. As shown in the figure, the life of a given vehicle being in service will typically extend considerably beyond the warranty period. Often, it is in the later years of the ownership experience that IVHM may become most valuable to the customers. In addition, it may be precisely then that the customers are considering their next replacement vehicle which makes it very important to the manufacturer as well. Of course, one of the big advantages of applying IVHM in the paradigm of real time optimization is that the available linkages back to manufacturing, validation, and product developments allow one to reap even greater rewards. Not explicitly shown in the figure but equally important are the linkages out to the supply chain for issues like coordination of spare parts availability, scheduling of service, or feeding requirements back into the supplier community whenever performance or quality issues arise.

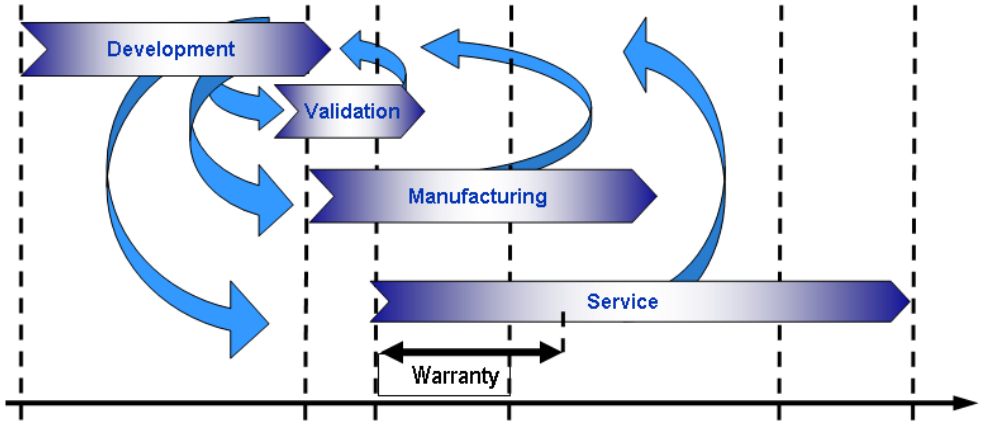

Fig. 3. Total Life Cycle Perspective

We generally consider our diagnostic and prognostic efforts in three broad categories which represent different situations—"enhanced diagnostics", "managed maintenance" and "prognostics". Some devices or systems do not warrant the application of sophisticated prognosis—they are well served by the ability to simply detect and diagnose the root cause of any problem . For example, very inexpensive items or extremely reliable items often fall in this class where the addition of sensors or software to prognose future behaviour may not be justified. These situations may still benefit from enhanced diagnostics. The managed maintenance area refers to the set of normal maintenance items on the vehicle. Instead of using traditional time or mileage based approaches to schedule maintenance, we instead use simple forms of prognosis to adapt the maintenance schedule to actual driving conditions and/or performance. A requirement for achieving low false positives is not necessary for this approach to do substantially better than pure time or mileage based approaches. Typically, we would still build in fairly conservative assumptions to mitigate concern for false negatives as well. Finally, areas including safety systems, fuel economy systems, emissions systems, or ones with sophisticated computer control are the target for advanced prognostics.

5. Sensor-Based Diagnosis & Prognosis

With the advent of higher and higher levels of electronics in today's products, there has been an increasing emphasis in on-board diagnosis to quickly detect faults and isolate their root cause[s]. The new technology frontier is clearly prognosis which adds the predictive element to what has gone before[5,6]. This new technology seeks to be able to identify problems before they happen so that corrective action can be taken prior to loss of service.

A primary focus is concentrated on key systems providing for enhanced safety, improved fuel economy, stringent emissions control, or hybridization/electrification of the vehicle. These kinds of systems are specifically targeted because of their obvious importance and because their successful implementation is typically dependent upon heavy use of electronics, controls technology and software (ECS) to achieve the required levels of performance. ECS systems can offer greater challenges in terms of both diagnostics and

prognostics. They typically require a stringent systems engineering approach, and this is precisely what IVHM methodologies can provide.

On-Board Diagnostic (OBD) systems were originally mandated by the US government to ensure that emissions systems were performing as mandated throughout the vehicle's life. Nearly all aspects of engine and transmission operation have the potential for impacting emissions levels. The current generation of on-board diagnostics known as OBD-II has been fully in operation since the 1996 model year of vehicles sold in the US. Over time, the use of these diagnostic systems has expanded well beyond just emissions control to today where you find sophisticated diagnostics being used throughout the vehicle.

With prognosis, we are raising the bar and need to be able to reliably determine the state of health (SOH) or remaining useful life (RUL) of key components or subsystems essential to the performance of the product. The emphasis on "reliably" here is very important as rough prognostic assessments are usually not actionable in the field. We need to ensure a low level of false positives and false negatives if we are to drive better decision making and thus achieve the benefit.

For onboard diagnostics, we use the term diagnostic trouble codes, or DTCs. In other industries, DTCs are referred to by other names such as Built-in Tests (BITs) but the concept is the same. A DTC is basically a software subroutine that runs at some appropriate interval and looks for indications of specific problems being present. A DTC subroutine typically begins with first verifying that a set of preconditions are satisfied before proceeding—this is to ensure that it is appropriate to run the desired check and that the needed parameters are available and defined. If the specific problem is detected, the DTC is set to an "on" state. Should a DTC be set to "on" incorrectly indicating a problem which is actually not present, this is referred to as a Type I error. This is the same as an "α error" or a false positive. Similarly, if a DTC fails to set and the problem is actually present, we call this a Type II error, or a "β error", or a false negative. In a simple case where the value of just a single parameter is being used to classify whether a given problem is present or not, you can imagine the situation with two overlapping distributions along that parameter's range of possible values as shown below in Figure 4. Ideally, the distributions would be widely separated but this is not always the case. The point at which you establish the parameter threshold value as shown below provides you a means to trade-off between Type I and Type II errors. A test with a high *specificity* has a low Type I (false positive) error rate. A test with high *sensitivity* has a low Type II (false negative) error rate. Let's consider the implications for an automotive example dealing with the vehicle's battery. If we have an assessment algorithm that generates very many false positives, we may be causing unnecessary battery replacements which in turn will result in the waste of both time and money. On the other hand, if our algorithm generates many false negatives, we risk inconveniencing the vehicle's owner by having the car not starting or operating properly. In the example below, the threshold has been set such that nearly all bad batteries are caught but at the expense of calling quite a few good batteries bad. In real applications, the classification is normally multidimensional.

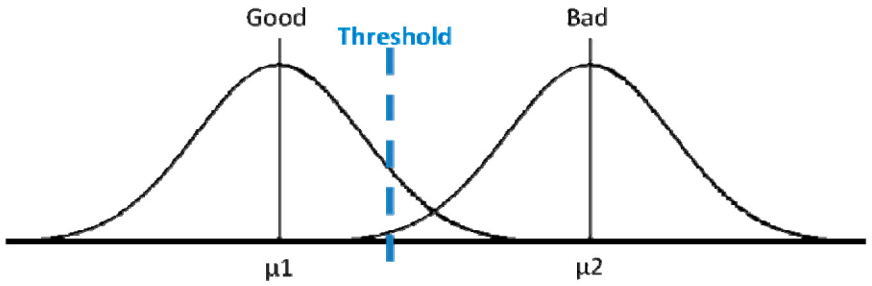

Fig. 4. Overlapping Distributions Forces Trade-off between False Positives & Negatives

Figure 5, as described by Professor Krishna Pattipati of the University of Connecticut, illustrates one conceptual view of the process for fault detection, fault isolation and control. There are many alternative ways to think about the problem. The model shown assumes that the system or subsystem being monitored makes available key sensory information or computed variables. These are in turn compared with expected or nominal values based on the operating regime of the system. The residuals or deviations can then be tested to provide input into an inference module that is preloaded with some kind of fault model. The results of these inferences together with the observed deviations allow an assessment of the problem severity. Finally, this can drive needed repairs or possibly real-time compensations to allow the system to maintain some minimum acceptable level of performance until such time as the ultimate repairs can be performed.

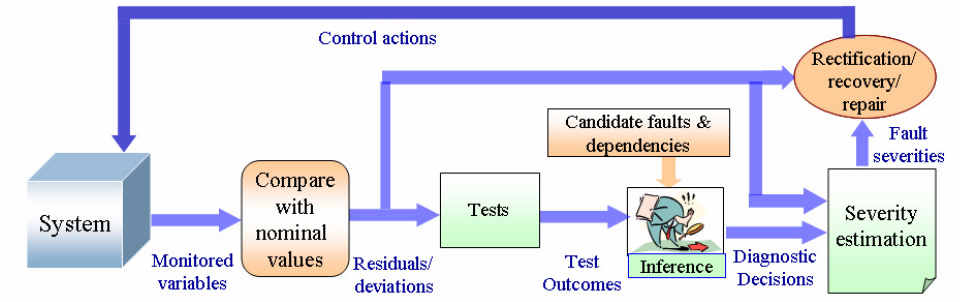

Fig. 5. Fault Detection, Isolation and Control

Most of the effort toward onboard diagnosis and prognosis has been pursued by using information available from within the operating vehicle itself. However, in cases where we can gather aggregate information from across an entire fleet of similar vehicles, we open up new possibilities that are not available with the just the vehicle specific information alone. For example, with aggregate fleet information, we are in a position to detect problems earlier in their life cycle while the total impact of those problems is still low and the cost of resolution is still correspondingly low. Further, if we were to look across the entire fleet and study performance of similar vehicles operating under similar driving conditions, we could learn useful information to send back to specific vehicles to focus performance monitoring on areas which were found to be at risk based on the overall fleet information.

6. Health Ready Supplier Components

In the context of automotive IVHM, no single company can or does make all components and subsystems for the final product as the consumer sees it. Cooperation with the global automotive supply base to clearly specify the kinds of information needed from the various subsystems to facilitate overall health management initiative goals and objectives must occur well in advance of the actual production needs, to allow for designing in of such features in an orderly and cost effective manner. This includes deciding what kinds of information are to be provided as outputs of the subsystem controllers, how often that data will need to be transmitted, how detailed it should be, and in what format it should be sent. Focusing on these important interface issues, should allow the OEM to more quickly and less expensively converge on a consistent framework to implement "health ready" components, resulting in a win-win-win situation for the automotive OEM, the suppliers and the customer. We recognize that various suppliers have invested a great deal of time and money to achieve their level of performance. This intellectual property is often unique to the specific supplier so careful attention must be paid to ensure that this intellectual property is protected and not allowed to be inadvertently communicated beyond its intended audience. It is to all constituents' advantage to protect the intellectual property and to encourage creativity and advancement of the health management capabilities. The specification and bidding process must be designed to ensure these needs are being met.

7. Future Directions

Integrated vehicle health management as it applies to the automotive industry is a specific example of how diagnostics and prognostics technology can improve the products we sell and enhance their value to our customers. This is of course precisely our goal. If one looks to different industries such as aerospace, rail, trucking, computers, data storage, printing, farm equipment, mining equipment, etc., we find many innovative examples of how prognosis is growing in application and importance. Together they provide a rich set of real world examples where solutions have been found relative to associated business issues, privacy issues, financial issues, etc.

This chapter began by looking at the evolution of the major paradigms in the automotive industry and how that positions us to peer into the future and envision how the new *real time optimization paradigm* opens up new opportunities. In a sense, it was the emergence of the web that provided the model for the new paradigm we have entered. Similarly, as we look to the evolution of the web itself, perhaps we can better see some of the future opportunities for IVHM. The original web applications (Web 1.0) were all static information displays. Web 2.0 which is now fairly common brought us more dynamic information and, very importantly, the ability of a large user community to share information in new ways. In the case of IVHM, this suggests tapping into fleets of vehicles which represent large comparison populations operating under similar conditions, in similar geographic environments, in similar climates, etc. This would allow us to go beyond what could ever be known or experienced by any single vehicle, to benefit from the richer experience of the full fleet of similar vehicles operating in similar conditions. Web 3.0 as it is currently conceived is intended to add semantic tagging to web based information – this along with some kind of reasoning capability opens the door for more effective use of the vast amount of available

data. This external reasoning will be very powerful in an IVHM context and allow us to effectively use both the vehicle specific information and the available aggregated population information more easily. Web 4.0 promises to deliver agent-based technologies which provide the needed foundation for enhanced automation and new kinds of services – being performed autonomously by remote computers without the need for as much human intervention. IVHM services will be created and deployed in a similar fashion to increase their effectiveness, speed their performance, and provide new services not feasible given today's technological limitations. The future is bright indeed.

8. Conclusions

The time has come to port integrated vehicle health management concepts originally pioneered in aerospace and other domains into the automotive industry.

- The successful automotive manufacturer must remain highly customer-focused to ensure delivery of high value at an affordable price.
- IVHM success will require partnering between the automotive manufacturer, its suppliers, as well as external technology providers located in private industry, academia and governmental labs ...on a global basis.
- IVHM applied to automotive products illustrates the power of the new real-time optimization paradigm which is emerging as the successor to the venerable lean paradigm.
- IVHM will require a fresh look at the associated business processes and systems which have evolved over the years.

9. Acknowledgments

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10. References

1. Wikipedia: http://en.wikipedia.org/wiki/Dewar_Trophy
2. Ford, Henry; with Crowther, Samuel, **My Life and Work**, Garden City, New York, USA: Garden City Publishing Company, Inc, ©1922
3. Ohno, Taiichi, **Toyota Production System: Beyond Large-Scale Production**, Productivity Press, ©1988
4. William J. Mitchell, Christopher E. Borroni-Bird and Lawrence D. Burns, **Reinventing the Automobile: Personal Urban Mobility for the 21st Century,** MIT Press, ©2010.
5. George Vachtsevanos, et al, **Intelligent Fault Diagnosis and Prognosis for Engineering Systems**, John Wiley & Sons, Inc., ©2006.
6. Michael G. Pecht, **Prognostics and Health Management of Electronics**, John Wiley & Sons, Inc., ©2008.