Diseases, Comorbidity, and Multimorbidity in Primary Care

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Primary Care Course
(Based on Cape Town, South Africa, 2007; and Barcelona, Spain, 2009)
The purpose of this presentation is to explore the concepts of “disease” and “chronic disease” and to show why the current focus on specific diseases runs counter to improving health and, especially equity in health, and to show why a continuum of care (“primary care”) for all people and populations is more appropriate than care for targeted diseases.
Diseases

• are professional constructs
• can be and are artificially created to suit special interests; the sum of deaths attributed to diseases exceeds the number of deaths
• do not exist in isolation from other diseases and are, therefore, not an independent representation of illness
• are but one manifestation of ill health

Sources:
A disease approach only gets at the manifestations of health disadvantage, and not at its roots. If there is any hope of reducing disease burden in the world, particularly in the rapidly emerging situation where almost no illness (except some with major dominant genetic origin) has a single “cause” and where almost every illness occurs as a result of multiple influences, a new paradigm for viewing ill health is necessary. “Diseases” are a professionally defined construct, often with no clear rules for assignment. The myriad and interacting influences depicted in the diagram “Societal Influences on Health” (see above) provide the basis for variation both in occurrence and progression of illness to “disease”. These terms come originally from the field of genetics, but are equally applicable to pathogenesis of diseases without an obvious genetic component.

Penetrance, which describe the situation where a “cause” of disease occurrence or progression is present but no disease or progression occurs

Pleiotropism occurs when a “cause” is present but can lead to more than one disease or more than one manifestation of progression

Etiologic heterogeneity occurs when a disease occurs as a result of exposure to any one of a number of “causes”.

Recognition of the variability in exposure to multiple influences of health makes the search for one “cause” (even a genetic “cause”), or even one treatment for a “disease” fruitless in the emerging environmental and social context of modern society.
This chart provides an example of etiologic heterogeneity – the phenomenon of any given disease or condition being influenced by more than one risk factor, i.e., diverse etiology. Of the 12 conditions selected for study with regard to their being influenced by different risk factors, ischemic heart disease, stroke, and diabetes are thought to be influenced by more than six of the 11 common risk factors selected for investigation. That is, numerous common risk factors are implicated in the occurrence of any given chronic disease.

For all but one condition (lung cancer), multiple risks are implicated, thus suggesting that “magic bullets” for the prevention of illness are unlikely to exist and showing the importance of interacting influences in the genesis and progression of illness.
Pleiotropism

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th># of Specific Diseases Associated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>9</td>
</tr>
<tr>
<td>Physical activity</td>
<td>7</td>
</tr>
<tr>
<td>Alcohol</td>
<td>7</td>
</tr>
<tr>
<td>Nutrition</td>
<td>7</td>
</tr>
<tr>
<td>Obesity</td>
<td>7</td>
</tr>
<tr>
<td>Hypertension (?)</td>
<td>3</td>
</tr>
<tr>
<td>Dyslipidemia (?)</td>
<td>2</td>
</tr>
<tr>
<td>Impaired glucose tolerance (?)</td>
<td>1</td>
</tr>
<tr>
<td>Proteinuria (?)</td>
<td>1</td>
</tr>
</tbody>
</table>


This chart shows the number of diseases associated with each of 9 common individual risk factors influential in the genesis and progression of the illness. Smoking is implicated in nine of the 12 specified diseases. Five of the 12 specified diseases are influenced by at least 7 of the risk factors. That is, numerous common chronic diseases share common risk factors. As the identified risk factors are hardly the totality of possible influences on disease, it is clear that pathways to the occurrence and progression of illness are very complex.
Diseases Change over Time

- Biological phenomena change the environment around individuals. (Lewontin, 2010)
- The environment changes the manifestation of diseases. For example, Clostridium difficile is a different disease in 2010 than it was in 1995. During just one decade, mutations in the bacterium have transformed the organism from “a rare nosocomial infection to one that can spread rapidly in hospitals and has spilled out into the community. Now, infection of healthy individuals with few or no risk factors is not uncommon”, and rates are increasing. (JAMA 2010)

Sources:
More than 60 studies found that standardized mortality rates across a range of serious mental disorders are 2-3 times greater than in the general population, with the majority of deaths attributed to medical illnesses. A growing list of risk factors for this excess are “unhealthy lifestyles, poor quality of medical care, poverty, biological mechanisms including dysregulation of the hypothalamic-pituitary-adrenal axis, and adverse metabolic consequences of psychotropic medications.”

Sources:
• “The genetics of mental illness may really be the genetics of brain development, with different outcomes possible, depending on the biological and environmental context.”

• “Although many of the genes implicated (in the genesis of illness) are involved in brain development, copy number variants do not appear to be specific for illnesses in the current diagnostic scheme. Genetic variants do not map selectively onto current diagnostic categories ... and the current diagnostic categories, based on clinical characteristics, do not seem to align well with findings from genetics and neuroscience.”

• “Although mental illnesses are more likely neurodevelopmental rather than neurodegenerative, the behavioral and cognitive manifestations ... may be late stages of processes that start early in development ...”; what may be required are novel interventions based on alternative plasticity or retraining circuitry rather than neurotransmitter pharmacology.

• IN OTHER WORDS, ILLNESSES ARE NOT DISCRETE ENTITIES; THEY RESULT FROM COMPLEX PROCESSES IN THE LIFE COURSE (INCLUDING FETAL). SIMILAR PHENOTYPES (DIAGNOSED “DISEASES”) HAVE DIFFERENT ETIOLOGIES (ETIOLOGIC HETEROGENEITY), REQUIRING DIFFERENT INTERVENTIONS.

How “chronic” are chronic diseases?
This slide includes diseases and conditions diagnosed by health professionals. Asthma and obesity are common diagnoses, each or both made in 5-10% of patients seen in a year in a health facility. Autoimmune disorders and seizures are less common (1-2% of patients seen in a year). Patients who receive these diagnoses are much more likely to have them diagnosed the next year (7-70% more likely). Currently, only two of these diagnoses are candidates for most “disease management” or “chronic disease care” programs.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Overall prevalence time 2</th>
<th>Prevalence among those having diagnosis in time 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>69</td>
<td>539 (x 7.8)</td>
</tr>
<tr>
<td>Asthma</td>
<td>70</td>
<td>628 (x 9.0)</td>
</tr>
<tr>
<td>Autoimmune disorder</td>
<td>18</td>
<td>641 (x 35.6)</td>
</tr>
<tr>
<td>Seizures</td>
<td>10</td>
<td>670 (x 67.0)</td>
</tr>
</tbody>
</table>

*per 1000, not adjusted for age
These four diagnoses are even more common than those in the previous chart: 10-20% of patients have them diagnosed in a year. Patients with these diseases or conditions diagnosed in a year are 4-5 times more likely to have them diagnosed in the subsequent year. Only two of the four (hypertension and lipid disorders) are candidates for most chronic disease management programs.
These seven diagnoses are at least as common as those in the previous chart: 15-35% of patients are diagnosed as having them in a year. They are also relatively likely to have them diagnosed in a subsequent year, although none of them are candidates for chronic disease management programs.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Overall prevalence time 2</th>
<th>Prevalence among those having diagnosis in time 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>URI</td>
<td>357</td>
<td>585 (x 1.6)</td>
</tr>
<tr>
<td>Pneumonia, non-bacterial</td>
<td>186</td>
<td>378 (x 2.0)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>231</td>
<td>525 (x 2.3)</td>
</tr>
<tr>
<td>Musculoskeletal s/s</td>
<td>190</td>
<td>461 (x 2.4)</td>
</tr>
<tr>
<td>Dermatitis, eczema</td>
<td>109</td>
<td>302 (x 2.8)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>116</td>
<td>326 (x 2.8)</td>
</tr>
<tr>
<td>Otitis media</td>
<td>136</td>
<td>452 (x 3.3)</td>
</tr>
</tbody>
</table>

*per 1000, not adjusted for age
Not all chronic diseases are manifested year to year.

Acute diseases sometimes behave as if they were chronic, recurring year to year.

Only a minority of common chronic diseases or conditions are currently candidates for the vast majority of chronic disease management programs.

Acute and chronic conditions share a characteristic: inflammation.
There is more variability in disease manifestations and persistence within diseases than across diseases because:

- diseases are not necessarily unique pathophysiological entities
- variability in diagnostic styles and practices
- presence of comorbidity
The challenges in primary care practice are person-focused rather than disease-focused. Most people have more than one health problem, increasingly as they age. Therefore, attention to health needs in primary care requires an awareness of the simultaneous presence of more than one health problem, which must be taken into account in providing person-focused care, at the very least in order to avoid conflicting management strategies.
Comorbidity is the concurrent existence of one or more unrelated conditions in an individual with any given condition. Multimorbidity is the co-occurrence of biologically unrelated illnesses.

For convenience and by common terminology, we use comorbidity to represent both co- and multimorbidity.
Socially disadvantaged people are more likely to have a large number of different diagnoses as compared with those who are more socially advantaged. This diagram shows that those enrolled in community health clinics for low-income people in the US are at least 3 times more likely to have more than 5 different types of diagnoses in a year. As socially disadvantaged people are less likely to receive adequate health care, the greater health disadvantage shown in this diagram is likely to be an underestimation of the increased morbidity among socially disadvantaged people.
In this chart, comorbidity, multimorbidity, and morbidity burden are separately identified. Although usually all are subsumed until the term “comorbidity”, there are subtle but important distinctions. Comorbidity, as used in the literature, originated as a term to denote the simultaneous presence of other and presumably un-related diseases in the presence of a particular disease, i.e., the presence of a mental health problem in a patient with cardiac disease.

Multimorbidity connotes the simultaneous presence of many separate diseases, each separately identified and sometimes summed to characterize people as to the number of diseases they have. Morbidity burden signifies the total burden of disease without regard to any particular disease. It therefore characterizes people and populations according to the total burden of diseases of different types. The major system for characterizing morbidity burden is the Johns Hopkins ACG (Adjusted Clinical Groups) (www.acg.jhsph.edu).
This graph, concerning people of age 65 and over in the US, shows that rates of hospitalization for causes that should be preventable by good primary care, rates of complications during hospitalization, and costs of care increase rapidly with increases in comorbidity (as measured by the number of types of chronic condition per person). That is, comorbidity is associated with higher costs, higher hospitalization for preventable conditions, and more adverse effects.

These data, from one province in Canada, show that there is little difference in resource use for people with only acute conditions, people with any chronic conditions, or people with only serious chronic conditions when the morbidity burden is the same. However, increasingly higher morbidity burden (i.e., more multimorbidity) is associated with progressively higher resource use, and the increase is the same regardless of the type of diagnosis (acute, chronic, major chronic). Chronic conditions alone do not, by themselves, imply high need for resources.

As thresholds for diagnosing disease are lowered over time, the variability within “diseases” will increase even further, as will the prevalence of multiple simultaneous or sequential diseases.
Diseases, Co- & Multimorbidity


<table>
<thead>
<tr>
<th>Treated Prevalence</th>
<th>Percentage Change, 1987-2002</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlipidemia</td>
<td>437</td>
</tr>
<tr>
<td>(Heart disease</td>
<td>9</td>
</tr>
<tr>
<td>Bone disorders</td>
<td>227</td>
</tr>
<tr>
<td>Upper GI problems</td>
<td>169</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>161</td>
</tr>
<tr>
<td>Mental problems</td>
<td>136</td>
</tr>
<tr>
<td>Diabetes</td>
<td>64</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>24</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>13</td>
</tr>
</tbody>
</table>


With progressively decreasing thresholds for diagnosis of disease, and possibly with real increases in some diseases, the prevalence of diseases under treatment is increasing rapidly throughout the world. This chart shows the very large increases in prevalence of particular diseases in the US in the fifteen years between 1987 and 2002. As this information comes from populations with private insurance, the estimates of prevalence undoubtedly understate the true prevalence of disease in the entire population, as people without insurance have more illness. In five of the 10 conditions, the prevalence has more than doubled in the fifteen years; in the case of hyperlipidemia, the prevalence has increased over four-fold. Thus, at the same time that mortality rates have been increasing, the treated prevalence of major illnesses has been increasing.
These data were obtained from medical and pharmacy claims data over 12 months from four companies, and included about 58,000 employees. Survey data about health and work performance were obtained from about 15,000 of these. The 27 most common conditions were selected and recorded if they were the primary diagnosis on the claims form.

This chart identifies the top ten health conditions occurring on medical claims and pharmacy claims. Conditions costing the most in terms of medical and pharmacy costs are in the left column; all but two are conventional biomedical diagnoses. The middle column shows that the most costly conditions in terms of lost productivity are primarily symptoms or signs; only three are conventional diagnoses. Lost productivity costs were more than four times medical and pharmacy costs. As a result, total costs reflected the occurrence of symptoms and signs rather than conventional medical conditions. That is, the mostly costly problems to employers are people's problems, not their diagnoses.
What is needed is person-focused care over time, NOT disease-focused care.
What Is the Appropriate Care Model?

- Primary care that meets primary care (not disease-specific) standards*
- Specialty referrals that are appropriate, i.e., evidence-based**
- Specialty care that meets specialty care standards**

*exist  **do not exist
Many studies in both industrialized and developing countries have provided the evidence to confidently conclude that health systems based on strong primary care are more effective and more equitable than health systems in countries with poorly organized primary care services and which rely predominantly on disease- and condition-oriented (i.e., specialty) health care.

PRIMARY HEALTH CARE “works” because it has definable system functions that provide the policy context for primary care.

PRIMARY CARE “works” because it has defined functions that include structural and process features of clinical health services that are known to improve outcomes of care.
• How valid/useful is the concept of chronic illness?
• Does it make sense to organize services around “chronic” illnesses?
• It is almost certain that morbidity, disability, and premature death are more likely in the presence of vulnerability to many types of illnesses. What are the implications for organization of health services?
• How can primary care and CCM be made complementary?
Is chronic care management pursuant to primary care or separate from it?

- Person-focused?
- Contributory to at least one of the four main features of primary care?
Is CCM part of primary care or separate from it?

- If the need for it is uncommon (as the data suggest), it is a referral function and not part of primary care.
- If the need for it is common, it is a way of enhancing some important and heretofore neglected element of care, possibly problem recognition.

Question: What critical process of care is served by CCM? Problem recognition? Follow-up and reassessment? If not, what?
Large medical groups that score higher in PRIMARY CARE ATTRIBUTES are more likely to score high on CHRONIC CARE MODEL elements. The primary care characteristics that are most related to the CCM score are

- COMPREHENSIVENESS of services (especially treatment of severe chronic illness and accepting financial risk for hospitalization)
- COORDINATION (problem list present in an electronic health record)

Implications of the Current Disease-Oriented Approach to Quality of Care and Payment for Performance

- Neglect of the problems of younger populations, especially children
- Neglect of quality of care and payment for performance in outpatient specialty care
- Failure to focus on inappropriate and unnecessary use
- Disease rather than person-focus
- Inadequate basis of evidence (non-generalizability to different populations; to people with multimorbidity; and to the influence of the way in which health services are delivered)
The management of the large percentage of people, especially the elderly, with high morbidity burdens should be returned to primary care, where care is person-focused, not disease-focused. Guidelines for the management of patients with multimorbidity are needed, in order to improve effectiveness of care, increase equity meeting health needs of socially-compromised populations, and reduce adverse events deriving from polypharmacy and other disease-specific interventions.
Any evaluation of enhancements to clinical primary care must consider the extent to which they better achieve the evidence-based primary care functions:

- First contact for new needs/problems
- Person (not disease) focused care (enhanced recognition of people’s health problems)
- Breadth of services
- Coordination (enhanced problems/needs recognition over time)
Deaths may be attributed to chronic diseases, but people still get sick from acute diseases and acute exacerbations.

Any enhancement of primary care has to deal with this reality.
Modern medicine is largely atheoretical. With the exception of a few rare genetic conditions, we do not understand why some people have greater susceptibility to disease and, particularly why some people are more prone to multimorbidity than other people. On the other hand, some people seem to be more resilient to health problems. Why?
It appears that there may be only a few “types” of medical problems, based on most predominant etiology:

- Infectious
- External injury
- Developmental/physical abnormality
- Mendelian dominant genetic
- Autoimmune
- Cellular degradation/degeneration

Question: If this is true or even only partly true, is the International Classification of Diseases a useful schema for classifying health problems? Might there be one that lends itself better to understanding etiology for the purpose of more effective prevention and treatment?
Are diseases really discrete categorizations of pathology?
Everyone knows that cardiovascular disease is the leading cause of death, but what is it?

It is “hypertensive DISEASES, ischemic heart DISEASES, rheumatic fever, pulmonary heart disease and DISEASES of the pulmonary circulation, OTHER FORMS of heart disease, cerebrovascular DISEASES or stroke, DISEASES of veins, lymphatic vessels, and lymph nodes, OTHER AND UNSPECIFIED DISORDERS OF THE CIRCULATORY SYSTEM, AND congenital MALFORMATIONS, or birth defects of the circulatory system.”

What and for whom is there benefit from calling it a disease – or the leading cause of death?

There appear to be many disorders included under the rubric of diabetes: insulin secretion; insulin transport; zinc-binding to insulin; and pancreatic islet beta cell development.

**IS DIABETES A DISEASE? DOES IT MAKE SENSE TO ASSUME THAT GUIDELINES FOR THE IDENTIFICATION AND MANAGEMENT OF DIABETES APPLY TO ALL “DIABETICS”?**

If the association between obesity and diabetes is absent in people with low concentrations of persistent organic pollutants, and the association becomes stronger as the concentration of these pollutants rises, is obesity a risk factor for diabetes? Is diabetes a single disease?

If a 90-year-old woman dies two months following hip fracture, did she die from an acute disease or a chronic disease? What is the “cause of death” likely to be coded as?
If oral contraceptives are protective on epithelial and non-epithelial cervical cancer but not on mucinous cervical cancer, is cervical cancer a single disease?

COPD is a chronic systemic inflammatory syndrome with complex chronic comorbidities. Patients with COPD mainly die of non-respiratory disorders such as cardiovascular disease or cancer.

COPD is a heterogeneous disease process. Although exacerbations of COPD, especially those defined as being infectious, are quite frequent, the number of randomized placebo-controlled trials of antibiotics is surprisingly small.

Sources:
Calverley PMA, Rennard SI. What have we learned from large drug treatment trials in COPD? Lancet 2007; 370(9589):774-785.
When occurring in the same individual, BMI greater than 30, systolic blood pressure greater than 140, and blood cholesterol greater that 250 mg/dL are associated with a six-fold increased odds of Alzheimer's disease.

What type of disease is Alzheimer's? What is the disease?

Hypothyroidism is three times more likely in women with rheumatoid arthritis than in the general population. Women with both conditions have a fourfold higher risk of cardiovascular disease than euthyroid women with arthritis, independent of conventional risk factors. Inflammation and autoimmunity are implicated in vulnerability to a wide variety of “chronic” diseases – and they may well be “acute”.

What Is a Chronic Disease?

Generally defined as persistence or recurrence, usually beyond one year.
Chronic Disease: Expanded Definition

- Incurable
- Complex “causation”
- Multiple risk factors
- Long latency
- Prolonged course
- Associated with functional impairment or disability

Of all global deaths in 2005, 60% were said to be caused by chronic diseases, principally cardiovascular diseases (32%), cancers (13%), and chronic respiratory diseases (7%). Data such as these are used to argue that chronic diseases are of growing and epidemic importance as causes of death.

Question: What is the appropriate target for the percentage of deaths in the world that are attributable to chronic diseases? Isn’t there a case to be made that perhaps ALL deaths should be due to chronic diseases, with acute illnesses falling towards zero percentage?

The greater the morbidity burden, the greater the persistence of any given diagnosis.

That is, with high comorbidity, even acute diseases are more likely to persist.
This diagram shows that as comorbidity increases, so does the likelihood of a repeat diagnosis of urinary tract infection (UTI) (which is generally not considered a chronic disease) in the year after a previous diagnosis. Those with a diagnosis of UTI in one year are not very likely to have it diagnosed in the subsequent year if they have little or no comorbidity, but are more likely to have a repeat diagnosis with increasing comorbidity. The same is the case for other conditions. That is, persistence of a health condition is more likely in the presence of other health conditions.