The Dynamics of Disease Progression in Sepsis: Markov Modeling Describing the Natural History and the Likely Impact of Effective Antisepsis Agents

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We conducted a 9-month prospective cohort study of 2,527 patients with systemic inflammatory response syndrome in three intensive care units and three general wards in a tertiary health care institution. Markov models were developed to predict the probability of movement to and from more severe stages—sepsis, severe sepsis, or septic shock—at 1, 3, and 7 days. For patients with sepsis, severe sepsis, and septic shock, the probabilities of remaining in the same category after 1 day were .65, .68, and .61, respectively. The probability for progression after 1 day was .09 for sepsis to severe sepsis and .026 for severe sepsis to shock. The probability of patients with sepsis, severe sepsis, and septic shock dying after 1 day was .005, .009, and .079, respectively. The model can be used to predict the reduction in end organ dysfunction and mortality with use of increasingly effective antisepsis agents.

A uniform set of definitions for sepsis and related syndromes was proposed in a consensus conference in 1991 [1]. For patients meeting criteria for the systemic inflammatory response syndrome (SIRS), the three terms proposed were sepsis, severe sepsis, and septic shock. SIRS was defined as two or more of the following: hypothermia or fever (temperature, <36°C or >38.5°C, respectively), tachycardia (>90 beats/min), tachypnea (>20 breaths/min), and leukocytosis (>12,000 WBCs/mm³), leukopenia (<4,000 WBCs/mm³), or an increase in the number of immature band forms (>10%). Sepsis was defined as SIRS plus a documented infection. Severe sepsis was defined as sepsis plus hypotension or peripheral manifestations of hypoperfusion abnormalities. Septic shock was defined as severe sepsis plus hypotension refractory to a 500-mL fluid challenge [1].

Sepsis, severe sepsis, and septic shock are not discrete disease identities but newly defined stages of the nonspecific systemic inflammatory response to major biological insults. Most of the biological insults result from infection [2]. Estimates of the frequency of the syndrome of sepsis in the United States range up to 500,000 cases a year [2]; 40% (200,000) of these patients develop septic shock. Septic shock accounts for 80,000 to 100,000 deaths per year [2] and is the most common cause of mortality in noncoronary intensive care units (ICUs) [3, 4]. The most recent data on vital statistics indicate that the entity septicemia represents the 13th leading cause of death in the United States, with an age-adjusted death rate of 7.9 per 100,000 population in 1993 [5].

In a prospective, hospital population–based study of sepsis [6], we found that the consensus conference definitions were consistent with the hypothesis of a hierarchical progression in patients from sepsis to severe sepsis and to septic shock. The evidence for the stages included the progressive increase in death rates of end organ dysfunction, proportion of patients with documented bloodstream infections, and mortality. We also observed that from 44% to 71% of patients in any category of the sepsis cascade had spent at least 1 day in the preceding state of the biological response syndrome before progression.

Once a disease is reasonably stratified into distinct stages, it is possible to define the transition rates for progression or regression from one stage to the other [7]. Multistate models have been used to define the probabilities of advancing from one stage to another in patients with cancer, diabetic retinopathy, or HIV infection [8, 9]. Models have also been used in other ways (e.g., for defining the duration of stages of disease by using laboratory markers such as CD4 T lymphocyte counts) [10]. Herein, we report the transitional probabilities for each of the stages of the sepsis cascade by using the multistate Markov model. We also used the model to define the theoretical reduction in morbidity and mortality with increasingly effective antisepsis agents as treatment of patients at any of these stages.

Methods

Patient Population

The University of Iowa Hospitals and Clinics (Iowa City) is a 900-bed teaching referral center where ~30,000 patients...
are admitted each year. During the study period (1 August 1992 to 30 April 1993), concurrent incidence surveys for the three putative stages of the syndrome of sepsis were performed on three ICUs and three wards. We surveyed 3,708 patients, of whom 2,527 met criteria for SIRS. The latter study cohort were followed up for a total of 30,126 days [6].

**Surveillance**

Prospective surveillance during the 9-month study was performed in a medical ICU with 12 beds, a surgical ICU with 24 beds, and a cardiovascular ICU with 13 beds. We also surveyed three general wards (a general surgery ward with 26 beds, a cardiothoracic surgery ward with 24 beds, and a medical oncology ward with 22 beds), which historically had had the highest incidence of nosocomial bloodstream infections [11].

Surveillance was performed by three experienced, specifically trained research nurses who visited all study units each weekday [6]. At the time of enrollment in the study, a special case report form was completed, on which demographic and clinical data were included. Patients were excluded from the study if they had been discharged from the ICU after a stay of <12 hours. All patients enrolled in the study were followed up for 28 days or until discharge from the hospital if it occurred before 28 days. Sepsis, severe sepsis, septic shock, and end organ dysfunction were included as end points. A high level of interrater reliability was obtained among study nurses (κ, 0.91; range, 0.6–1.0), with a sensitivity of 85% and a specificity of 96% for recording data [6].

**Definitions of the Biological Response to Infection and End Organ Dysfunction**

The definitions that we employed for SIRS, sepsis, severe sepsis, and septic shock were adapted from those reported by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference [1]. We also noted if patients met only two, three, or all four of the components of SIRS [6]. Definitions of end organ dysfunction have been described previously [6, 12, 13].

**Statistical Analysis**

The Markov chains model is a probability model based on the development of a transition matrix that describes the likelihood of change from one stage to another. In developing the model, the specific stages, the time intervals of interest, and the absorbing or final stages in the continuum are defined [7]. Markov models assume that a patient is always in one of a finite number of discrete health states, called Markov states. The ability of the Markov model to represent repetitive events and the time dependence of both probabilities and utilities allow for accurate representation of clinical settings [14]. A matrix is defined with the sequential stages listed individually from top to bottom: these are the stages at the starting point of the analysis. The final stages, attained at defined intervals, are listed from left to right. Then either the number of people who have moved from one stage to the next or the probability of moving from one stage to the next over a specific time frame can be examined. In the model presented herein, we specifically examined transition for 1, 3, and 7 days.

We constructed a Markov matrix by referencing the starting point and examining three stages of interest (sepsis, severe sepsis, and septic shock) as well as the two absorbing states (discharge and death). Progression both forward or backward from one stage to another as shown in figure 1 can be envisaged. For example, an individual might move from severe sepsis to septic shock or from septic shock back to severe sepsis. In the Markov process, an absorbing state is defined as a state from which no transition to other states can occur (e.g., death). Following Beck and Pauker [7], transition rates from stage to stage were calculated from the observations by using the formula

\[ P_{ij} = \frac{N_{ij}}{N_i} \]

where \( N_{ij} \) is equal to the number of transitions over two consecutive days from stage \( i \) to stage \( j \) and \( N_i \) is equal to the total number of person transition days for stage \( i \). Once again, following Beck and Pauker [7], the transition probability is calculated as

\[ P_{ij} = 1 - \exp(-RT) \]

where \( R \) equals the transition rate and \( T \) is the time period (\( T = 1, 3, \) or 7 days).

In our calculations, we determined daily transition probabilities; the total number of patient-days was 30,126. These calculations for a 1-, 3-, or 7-day time interval or any time interval of interest can also be performed. The Markov process is an example of a stochastic process that has a special property. The Markov property states that the probability that an individ-

![Figure 1. Transitional probability of the sepsis cascade. The open circles indicate the starting stages (no systemic inflammatory response syndrome [SIRS], SIRS, sepsis, severe sepsis, and septic shock). The arrows represent forward or backward progression from one stage of the sepsis cascade to another or from one stage to an absorbing state (rectangles). The probabilities of advancing to a more advanced stage or regressing to a less severe stage of the sepsis cascade or to an absorbing state are calculated by the Markov model. SIRS was defined as two or more of the following: hypothermia or fever (temperature, <36°C or >38.5°C, respectively), tachycardia (>90 beats/min), tachypnea (>20 breaths/min), and/or leukocytosis (>12,000 WBCs/mm³), leukopenia (<4,000 WBCs/mm³), or an increase in the number of immature band forms (>10%).](cid.oxfordjournals.org)
Table 1. Transition probability matrix for stages of the sepsis cascade.

<table>
<thead>
<tr>
<th>Stage at start</th>
<th>No SIRS</th>
<th>SIRS</th>
<th>Sepsis</th>
<th>Severe sepsis</th>
<th>Septic shock</th>
<th>Discharge</th>
<th>Death</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. 1 d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No SIRS</td>
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<td>.3184</td>
<td>.0284</td>
<td>.0075</td>
<td>.0064</td>
<td>.1524</td>
<td>.0184</td>
<td>1</td>
</tr>
<tr>
<td>SIRS</td>
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<td>.7650</td>
<td>.0074</td>
<td>.0116</td>
<td>.0021</td>
<td>.0331</td>
<td>.0100</td>
<td>1</td>
</tr>
<tr>
<td>Sepsis</td>
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<td>.0307</td>
<td>.6485</td>
<td>.0916</td>
<td>.0042</td>
<td>.0310</td>
<td>.0046</td>
<td>1</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>.1050</td>
<td>.0423</td>
<td>.1204</td>
<td>.6841</td>
<td>.0263</td>
<td>.0130</td>
<td>.0089</td>
<td>1</td>
</tr>
<tr>
<td>Septic shock</td>
<td>.0390</td>
<td>.0272</td>
<td>.0331</td>
<td>.2050</td>
<td>.6072</td>
<td>.0092</td>
<td>.0793</td>
<td>1</td>
</tr>
<tr>
<td>B. 3 d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No SIRS</td>
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<td>.3386</td>
<td>.0402</td>
<td>.0187</td>
<td>.0064</td>
<td>.1524</td>
<td>.0184</td>
<td>1</td>
</tr>
<tr>
<td>SIRS</td>
<td>.3106</td>
<td>.6894</td>
<td>.0297</td>
<td>.0627</td>
<td>.0080</td>
<td>.0416</td>
<td>.0082</td>
<td>1</td>
</tr>
<tr>
<td>Sepsis</td>
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<td>.4502</td>
<td>.5460</td>
<td>.0872</td>
<td>.0106</td>
<td>.0491</td>
<td>.0082</td>
<td>1</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>.1688</td>
<td>.0912</td>
<td>.1449</td>
<td>.5249</td>
<td>.0249</td>
<td>.0232</td>
<td>.0148</td>
<td>1</td>
</tr>
<tr>
<td>Septic shock</td>
<td>.0962</td>
<td>.0511</td>
<td>.0928</td>
<td>.3124</td>
<td>.4004</td>
<td>.0037</td>
<td>.0404</td>
<td>1</td>
</tr>
<tr>
<td>C. 7 d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No SIRS</td>
<td>.6404</td>
<td>.3596</td>
<td>.0515</td>
<td>.0229</td>
<td>.0015</td>
<td>.1094</td>
<td>.0034</td>
<td>1</td>
</tr>
<tr>
<td>SIRS</td>
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<td>.0509</td>
<td>.0627</td>
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<td>.0888</td>
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<td>.0007</td>
<td>.0689</td>
<td>.0075</td>
<td>1</td>
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<tr>
<td>Severe sepsis</td>
<td>.2108</td>
<td>.1562</td>
<td>.1358</td>
<td>.4059</td>
<td>.0282</td>
<td>.0387</td>
<td>.0150</td>
<td>1</td>
</tr>
<tr>
<td>Septic shock</td>
<td>.1885</td>
<td>.1364</td>
<td>.1287</td>
<td>.2674</td>
<td>.2309</td>
<td>.0132</td>
<td>.0349</td>
<td>1</td>
</tr>
</tbody>
</table>

NOTE. SIRS = systemic inflammatory response syndrome. Matrix of probabilities for the five sequential stages (no SIRS, SIRS, sepsis, severe sepsis, and septic shock) and the two absorbing stages (discharge being alive and death) are presented. Numbers are probabilities after 1, 3, and 7 days. Stages at start are listed from top to bottom, and final stages attained at different intervals are listed from left to right. Probabilities refer specifically to the probability of moving from one stage to the next over the specified time frame. For example, in part A, .6816 (no SIRS, no SIRS) refers to the probability of staying in this stage (no SIRS) over a 1-day period; similarly, .0916 (sepsis, severe sepsis) in part A refers to the probability of advancing from sepsis to severe sepsis after 1 day. Probabilities have been rounded off in the text for further clarity.

Results

During the 9-month period, 2,527 (68%) of the 3,708 patients admitted to the surveyed wards met the criteria for SIRS. The more criteria for SIRS with which the patients presented, the higher the probability for having evidence of infection and thus meeting criteria for sepsis after 1 day (RR: 1.0, 1.37 [95% CI, 0.87–2.17], and 2.03 [95% CI, 1.20–3.46]) for two, three, and four criteria, respectively ($\chi^2$ for linear trends, 6.94; $P = .008$). By 1 day, between 61% and 68% of patients in any stage of the sepsis cascade (sepsis, severe sepsis, or septic shock) remained at the same level, and between 3.1% and 21% progressed to a less severe stage (table 1, part A). Nine percent of those with sepsis progressed to severe sepsis, and 2.6% initially with severe sepsis had progressed to septic shock. After 3 days, between 40% and 55% of patients with sepsis, severe sepsis, or septic shock remained in the same stage (table 1, part B). It is noteworthy that from 6.9% to 31% of patients improved. Of those patients with sepsis, 8.7% developed severe sepsis; of those with severe sepsis, 2.5% developed septic shock. After 7 days, between 23% and 45% of patients in any of the three stages remained in the same stage (table 1, part C). Of those patients with sepsis and severe sepsis, 8.1% and 2.8%, respectively, progressed to a more severe stage, whereas of those with sepsis, severe sepsis, and septic shock, 12%, 14%, and 27%, respectively, regressed to a less severe stage.

The mortality rate was higher as more criteria of SIRS were met. The highest mortality rate was among patients with septic shock after 1 day (7.9%), decreasing after 3 days (4.0%) and 7 days (3.5%) (figure 2). We also calculated the probability of developing severe sepsis, septic shock, or death after meeting criteria for sepsis, independently of the day that it happened; the probabilities were .72, .17, and .16, respectively. Similarly, the overall proportions of individuals who developed end organ dysfunction were as follows: adult respiratory distress syndrome, 4.6%; acute renal failure, 13.9%; and disseminated intravascular coagulation, 13.9%.

The data can be used to predict what would be the effect of an antisepsis agent that was increasingly effective in decreasing the probability of moving to a more severe stage of the sepsis cascade. For example, with use of the transition rate, the effect...
of an antisepsis agent with a 50% effectiveness for preventing patients with sepsis from advancing to severe sepsis could be crudely estimated; the model predicts that the probability of death would fall from .16 to .08. Similarly, the probability of developing severe sepsis would decline from .72 to .36.

Discussion

Some reasons for constructing multistate models are to provide a comprehensive view of a disease process, to allow an estimation of the proportions of individuals who will be in the various stages at some time in the future, and to make more efficient use of incomplete information when only small proportions of individuals’ disease histories are available [15]. Such multistate models have been used to explain the natural history of diverse diseases. Markov chains demonstrated that 25% of observations of diabetic retinopathy will change from grade 1 to grade 5 or 6 in 17 years and that 25% will change from grade 2 to grade 5 or 6 in 16 years [16]. For patients infected with HIV, the Markov model helped to estimate the interval (4.1 years) between seroconversion and a CD4 cell count persistently <500/mm^3 but >349/mm^3 [10]. The interval between HIV seroconversion and a CD4 cell count of <200/mm^3 was estimated at 8 years.

Previously, the term sepsis syndrome was somewhat confusing, and new definitions were proposed on the basis of the hypothesis of a hierarchical continuum. In a prospective, observational study [6], we developed data supporting the hypothesis. Among patients with SIRS, 26% (649 of 2,527) developed sepsis, 18% developed severe sepsis, and 4% developed septic shock. However, the recently described stages of SIRS did not provide information on the probability of advancing or regressing from one stage to the other. These calculations may be important for predicting the individual probabilities of developing a more severe stage of the biological response or in estimating the change in probability with effective therapy.

As previously reported [6], a progressively higher mortality rate was observed as more severe inflammatory response criteria were met. The 28-day mortality rates among patients with sepsis, severe sepsis, and septic shock were 13%, 18%, and 46%, respectively. In the present analysis, for patients with septic shock, the probability of death after 1 day was .079 and decreased 51% after 3 days and 44% after 7 days, thus indicating that the highest probability of dying was in the first 3 days. Sixty-five percent of the patients with sepsis remained in the sepsis stage after 1 day, but only 55% and 45% remained in the sepsis stage after 3 and 7 days, respectively. Moreover, the probability of progressing to severe sepsis was .092, .087, and .081 after 1, 3, and 7 days, respectively; the probability of improving was .031, .069, and .12 after 1, 3, and 7 days, respectively. It appears that as more days passed, the probability of improving was higher. These data stress the importance of early intervention to prevent the progression to more advance stages or death in patients in the sepsis cascade, in particular in those with septic shock.

Transitional probabilities can also be used to compare the effectiveness of two or more treatments, when end points other than mortality are of interest. End points of interest could be the length of time (days in this case) within a determined stage or the probability of advancing to the next more severe stage of disease. This could be particularly important in therapies for sepsis that could decrease the probability of developing end organ dysfunction. Similarly, effective therapies might reduce the duration (days) in a relatively severe stage of sepsis, and evolving organ dysfunction that develops in the course of sepsis markedly influences the outcome of critically ill patients [13]. Interventions aimed at improving the quality of care could be measured in the decreased number of days that patients are in a particular stage with defined end organ dysfunction; for example, the timely administration of effective antibiotics and the prevention, early identification, or management of complications could be important variables in comparisons of care between different institutions after controlling for case-mix differences. Furthermore, cost analysis may be refined if certain stages were found to be more expensive than others. The examples cited are not intended to oversimplify the effect of a single therapy on the outcome of sepsis, but the ability to calculate the single effect of each of the interventions will help with the decision-making process of specific interventions.

In the last 5 years, a number of immunotherapies for sepsis have been tested in clinical trials [17–25]. In general, the clinical trials have been conducted without a clear understanding of the natural history of sepsis. Furthermore, there were no models by which to predict the potential history of SIRS [6]. Herein, we illustrate with Markov modeling the natural history of the syndrome of sepsis and the potential benefits of effective antisepsis therapies.
Appendix 1
Definitions of SIRS

SIRS is defined as two or more of the following: temperature of \(> 38.5^\circ\text{C} \) or \(< 36^\circ\text{C}\); heart rate of \(> 90\); respiratory rate of \(> 20\); and/or a WBC count of \(> 12,000/\text{mm}^3\) or \(< 4,000/\text{mm}^3\) or \(> 10\)% immature band forms. Sepsis is defined as SIRS plus a documented infection (positive culture for organism). Severe sepsis is defined as sepsis associated with organ dysfunction, hypoperfusion abnormalities, or hypotension. Hypoperfusion abnormalities include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. Septic shock is defined as sepsis-induced hypotension despite fluid resuscitation plus hypoperfusion abnormalities.

Appendix 2
The Markov Model

The Markov model is an example of a stochastic process in which the dynamics of the process enable the calculation of the probability of moving from one disease state to another over a specific time period. The specific modeling for the Markov process first requires that a set of distinct mutually exclusive and exhaustive disease states be identified. A patient can be thought to be in one of these states at a particular time, and it is of interest to determine or calculate the probability of moving to another disease state over some specific time period. The initial time and the next time can be conceptualized as time \(i\) and time \(i + 1\), respectively. If a patient is followed up over some time period, such as 28 days, the distinct transitions from day 1 to day 2, from day 2 to day 3, and so on can be imagined. With the Markov process, the transition probability from one state to another over these daily time intervals is assumed to be dependent only on the state that the patient is in at time \(i\) (i.e., the probability of moving from one state to another from time \(i\) to time \(i + 1\) is assumed to depend only on the person’s state and time \(i\) and is completely independent of the history that led the person to be in a state at time \(i\)). This is a very strong assumption; however, this assumption does simplify the statistical modeling considerably since transition probabilities, such as daily transition probabilities, can be calculated by utilizing all the transitions over the time period of interest.

Some of the states in the Markov process may be absorbing states. These are states from which an individual cannot depart. Death is an example of an absorbing state. Once a patient dies there is no transition from that state, and the probability of staying in the death state from time \(i\) to time \(i + 1\) is therefore equal to 1. Other states are referred to as nonabsorbing states.

The primary calculations in the Markov process involve calculations of the rate of transition from one state to another over the prescribed time interval (e.g., over 1 day). Once these rates are calculated on the basis of person-days of transition, then probabilities of transition can be calculated by converting these disease rates to disease probabilities with use of the expression \(P = 1 - \exp(-RT)\), where \(P\) is the transition probability and \(R\) is the transition rate calculated on the basis of person-days of transition. Beck and Pauker [7] provide a complete description of the calculation of these probabilities and the utilization of transition rates calculated on the basis of person-days of transition. For the present study, calculations were done by using several different time periods, first for 1-day transitions, second for 3-day transitions, and third for 7-day transitions.

References


