Appendix A

GOS, GOSE, DRS

Resuscitation Outcomes Consortium

Scoring

GOS: The overall rating is based on the lowest outcome category indicated

1 dead
2 vegetative state (VS)
3 severe disability (SD)
4 moderate disability (MD)
5 good recovery (GR)

GOS-extended: The overall rating is based on the lowest outcome category indicated:

1 dead
2 vegetative state (VS)
3 lower severe disability (Lower SD)
4 upper severe disability (Upper SD)
5 lower moderate disability (Lower MD)
6 upper moderate disability (Upper MD)
7 lower good recovery (Lower GR)
8 upper good recovery (Upper GR)

DRS: Score is based upon point total

# points	Level of disability
0	None
1	Mild
2-3	Partial
4-6	Moderate
7-11	Moderately Severe
12-16	Severe
17-21	Extremely severe
22-24	Vegetative state
25-29	Extreme vegetative state
30	Death

Appendix B

Structured Interviews for GOS and GOSE

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Structured Interviews for the Glasgow Outcome Scale and the Extended Glasgow Outcome Scale: Guidelines for Their Use

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ABSTRACT

The Glasgow Outcome Scale (GOS) is the most widely used outcome measure after traumatic brain injury, but it is increasingly recognized to have important limitations. It is proposed that shortcomings of the GOS can be addressed by adopting a standard format for the interview used to assign outcome. A set of guidelines are outlined that are directed at the main problems encountered in applying the GOS. The guidelines cover the general principles underlying the use of the GOS and common practical problems of applying the scale. Structured interview schedules are described for both the five-point GOS and an extended eight-point GOS (GOSE). An interrater reliability study of the structured interviews for the GOS and GOSE yielded weighted kappa values of 0.89 and 0.85, respectively. It is concluded that assessment of the GOS using a standard format with a written protocol is practical and reliable.

Key words: Glasgow Outcome Scale; outcome assessment

INTRODUCTION

The Glasgow Outcome Scale (GOS) (Jennett and Bond, 1975) has become the most widely used scale for assessing outcome after head injury and nontraumatic acute brain insults. Despite its popularity, the GOS is increasingly recognised to have important shortcomings (Anderson et al., 1993; Gouvier et al., 1986; Grant and Alves, 1987; et al., 1985; Maas et al., 1983). The aim of the present paper is to argue that many of the main criticisms may be overcome by adopting a standard, well-specified format for the interview, and by being clear about the purposes and limitations of the GOS assessment. A set of guidelines are proposed for using the GOS and the extended GOS, and information is given concerning the reliability of the structured interviews.

ADDRESSING LIMITATIONS OF THE GOS

Traditionally, outcome on the GOS has been assigned after a short interview, usually unstructured, and not involving a written protocol. This open-ended format encourages impressionistic use of the scale; the results are variable among individual assessors (Maas et al., 1983), and there is evidence of systematic bias between different professional groups (Anderson et al., 1993). The upper levels of the GOS are multidimensional, and the criteria for the upper categories are therefore ambiguous (Grant and Alves, 1987). The approach described below attempts to overcome such problems by adopting a standard format for the interview and identifying specific criteria for assigning an outcome category. The major categories of outcome used in the present structured

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interviews (Appendix) follow closely the descriptions of the Glasgow Outcome Scale provided by Jennett and Bond (1975), Jennett et al. (1981), and Jennett and Teasdale (1981). The questionnaires are designed to achieve greater objectivity and reliability than the traditional method of assigning an outcome category.

The GOS is sometimes interpreted as emphasizing physical rather than cognitive and emotional problems (Anderson et al., 1993). In fact, Jennett and Bond (1975) and Jennett et al. (1981) pointed out that mental change was more important than physical limitation in determining disability after head injury. However, in practice this precept is often overlooked: thus, Good Recovery may be taken to be physical independence in the absence of neurological deficits (Hütter and Gilsbach, 1993). In constructing the questionnaires, we used the aspect of social disability described by Jennett et al. (Jennett and Bond, 1975; Jennett et al., 1981; Jennett and Teasdale, 1981), including effects on social and leisure activities and disruption to family and friendships. This approach will necessarily assign fewer patients to the Good Recovery category than an interpretation restricted to physical or neurological limitations, but is more faithful to the original concept of social disability.

The GOS has also been criticized because there are no guidelines for dealing with commonly encountered problems, including the effects of extracranial injury, epilepsy, and preinjury unemployment (Anderson et al., 1993; Boake, 1996). These specific issues are discussed below, and suggestions are made for resolving the difficulties that can arise.

It is often commented that the GOS categories are broad, and the scale is therefore insensitive to subtle changes in functional status (Gouvier et al., 1986; Hall et al., 1985; Hall, 1992). Jennett et al. (1981) suggested that the GOS can be extended by dividing each of the upper three categories into "better" and "worse," but did not give criteria for making these distinctions. Several schemes for extending the GOS have been suggested (Horne and Schremitsch, 1989; Livingston and Livingston, 1985; Maas et al., 1983; Smith et al., 1979), but a general consensus has not emerged. The eight-point, extended Glasgow Outcome Scale (GOSE), develops the proposal of Jennett et al. (1981) by providing various criteria to subdivide the upper three categories of the scale. These criteria evolved through pilot work, and, in the final version, they are easy to apply and reliable, and give a division of the patients in each category. The questionnaires used to obtain the GOS and GOSE are identical apart from the inclusion of the additional items in the GOSE.

There are many contexts in which a more detailed assessment of specific limitations and their effects than that provided by either the GOS or GOSE is appropriate and desirable. The precise neurological, neuropsychological, emotional, and behavioral indices used will depend on the purpose of the assessment and the resources available to carry it out. An issue not fully resolved is the best choice of tests to supplement the GOS when it is adopted as a primary end point: sensible decisions require an understanding of the relationship between the GOS and other measures of impairment and disability.

GUIDELINES FOR STRUCTURED INTERVIEWS FOR THE GOS AND GOSE

Purpose of the GOS

The Glasgow Outcome Scale was developed to allocate people who have suffered acute brain damage from head injury or nontraumatic brain insults into broad outcome categories. The scale reflects disability and handicap rather than impairment; that is, it focuses on how the injury has affected functioning in major areas of life rather than on the particular deficits and symptoms caused by injury (World Health Organization, 1980). It is not intended to provide detailed information about the specific difficulties faced by individual patients, but to give a general index of overall outcome. It is of particular value in allowing the outcome of different groups of patients to be compared in a simple and easily interpreted fashion (Marshall, 1987). It has been recommended as a measure of outcome for clinical trials (Clifton et al., 1992) and has been widely adopted for this purpose.

Principle Areas Requiring Judgement

The questionnaires are designed to be used in a structured interview, and some background knowledge is necessary in order to administer the scale. Areas that may sometimes involve exercise of judgement can be summarized in four rules for applying the GOS:

1. Disability due to head injury is identified by a change from preinjury status. The scale is designed to assess changes and restrictions that have taken place as a result of head injury. Questions are included concerning preinjury status because pilot work indicated that this was a major confounding factor when determining outcome in the general head-injured population. In research samples, patients with premorbid difficulties are often excluded, and the issue of preinjury status may be less salient. The inclusion of questions concerning preinjury status makes it possible to assess preexisting disability and to make appropriate qualifications on the assessment of outcome after head injury; there are more detailed instructions under "scoring" below.

2. Only preinjury status and current status should be considered. The person's initial state after injury and hopes for the future are not relevant in determining outcome. "Current" status includes problems and capabilities evident over the past week or so. Some patients are more severely injured than others, and some seem to make a "remarkable" recovery considering their initial state. Nevertheless, as previously stated, a patient should not be said to have made a good recovery "considering how bad he was" (Jennett et al., 1981). Such considerations are not relevant in determining outcome, because it is the level reached that is important, and the severity of initial injury should not be taken into account. For research studies, it is recommended that the person who is assigning the GOS not be someone who has been involved in the acute care of the patient (Anderson et al., 1993). Similarly, interview at a stage when there has recently been relatively rapid improvement in the patient's state may produce an overoptimistic view, because there is an expectation of continuing recovery in the future. It is important to establish current capabilities independently of hope for future progress.

3. Disability must be a result of mental or physical impairment. The injury is an event that has occurred at a particular time, but not all changes that have taken place following the event will be due to the injury. Thus, if a patient is capable of performing the activity but does not do it for some reason they are not considered disabled. For example, the patient's financial circumstances may have changed, and this can produce a restriction in lifestyle. The precise question that is being asked is sometimes hypothetical: what exactly is the patient capable of even though they do not actually do it? If the answer to a question indicates that the head-injured person has some difficulty in a particular area, then it may be necessary to probe more deeply. After most of the main questions is a note amplifying the hypothetical issue that is being addressed, and there are further notes below. If necessary, the questioning should be continued to determine the answer to the hypothetical question.

4. Use the best source of information available. A necessary limitation of the approach is that it relies on verbal report, and much of the time the information provided will have to be taken at face value. However, it is important to remain aware of the circumstances in which information given is likely to be misleading, and the practical steps that can be taken to improve the quality of information: (a) In some cases a patient will lack insight, and whenever possible a relative or close friend of the head injured person should also be interviewed (Anderson et al., 1993; Jennett et al., 1981; McKinlay and Brooks, 1984). Patients are particularly likely to deny psychological changes, but it should be noted that there is also some evidence that relatives who are "worriers" may overreport postinjury problems (McKinlay and Brooks, 1984). The questionnaire is worded so that it can be used either with the patient or with a caregiver or relative, and information can be recorded separately from these sources if desired. (b) Particular indices such as return to work should not be given too much weight (Jennett et al., 1981). Enquiry may reveal that special arrangements have been made by an employer to accommodate the patient or that the patient is capable but work is lacking. (c) Responses that are contradictory or inconsistent indicate the need to explore more deeply or find another informant. (d) We recommend that the complete questionnaire be normally administered, because sometimes responses to later items can indicate the need to go back and question more thoroughly on earlier points or reevaluate the significance of earlier answers. For example, occasionally, a patient will give responses that indicate that they have specific problems with shopping or travel, but subsequent questioning indicates that they have returned to work, or normal social and leisure activities. Further consideration may indicate that such a person should be considered to be moderately disabled rather than severely disabled, that is, that they are capable of activities of independence outside the home, even if they have some difficulties with them.

Other Considerations

Risk of epilepsy. A patient may be prevented from driving after head injury because there is a risk of late epilepsy, although the person has not actually had a seizure. The restriction on driving may interfere with return to previous employment and other aspects of return to normal life even when the patient has otherwise made a complete recovery. We suggest that in these cases the restriction should be ignored for the purposes of determining an overall score on the GOS/GOSE. On the other hand, if the patient has actually suffered a seizure, then restrictions imposed by the risk of epilepsy should be taken into account.

Effect of head injury versus effects of other injuries or illness. Although the scale is directed at the effect of brain injury, it does not itself distinguish changes due to injury to the brain from disability caused by injury to other parts of the body. Some patients with multiple injuries may have lost functioning due to injuries to the limbs. Depending on the purposes for which the scale is used, it may be important at the time of interview to distinguish any such effects from those caused by brain injury. Anderson et al. (1993) found that general practitioners may assign GOS score on the basis of physical disability independent of head injury. It is usually relatively easy to

discount any minor effects of injury to other parts of the body. However, in some cases when such injuries are severe, for example, major spinal injury, it will be difficult to assign a GOS that reflects only the effects of head injury. This should be noted appropriately when reporting the GOS.

Age Range

The GOS has customarily been used with both adults and children. However, the reliability of the GOS applied to children is unknown; in the case of very young children, the GOS criteria appear to be largely inapplicable. The current approach is designed for use with people aged 16 years and upwards.

Timing of Assessment Post-injury

The scale is intended for use after discharge from hospital, and, in particular, moderate disability and good recovery are not assessable until after discharge. Reports should always include the timing of assessment.

Assigning an Outcome Category

The GOS and GOSE are simple hierarchical scales in which the patient's overall rating is based on the lowest outcome category indicated. Outcome categories are given in brackets on the right side of the questionnaires.

Severe disability. Obtain answers to all the main questions concerning independence and the questions concerning preinjury problems in these areas (Q2–Q4). If the patient was fully independent before the injury, and the answers to one or more of the dependence questions indicate that this is no longer the case, then they are Severely Disabled (SD).

Moderate disability. Obtain answers to all the main questions concerning disability, and the questions concerning preinjury problems (Q5–Q7). If the patient had no prior problems and the answers to one or more of the questions concerning current difficulties indicate that this is no longer the case, then they are Moderately Disabled (MD). If the patient had prior difficulty in one or two of the areas, then they can usually be rated on the basis of the answers to the remaining questions. Sometimes a patient will have had prior problems, but these have become markedly worse as a result of injury, and this change can be used in rating. If the person was unemployed and not seeking work before the injury, then they should be rated on the answers given to questions 6 and 7. For example, if the person is long-term unemployed or retired, then they should be rated on social and leisure activities and personal relationships. Question 6c is included because people may have a very restricted preinjury social repertoire (for example, the chronically ill or people who are socially isolated), and it may not be sensible to rate them on this question. In general, it is not uncommon for people to have preinjury difficulties in one or two of these areas, and it will usually be possible to determine an outcome on the basis of the other questions.

Good recovery. If the patient does not fulfill the criteria for any of the lower outcome categories, then they are considered to be a Good Recovery. Note that the "Good Recovery" category includes people with minor disability. On the GOSE, patients with minor disability are assigned to the lower band of Good Recovery, and those without any head injury related disability to the upper band.

Preinjury disability. There are some cases that are problematic because of the presence of very significant preinjury problems and severe preinjury dependency. Such cases will be excluded from studies aimed at researching the nature of the effects of injury on the brain but must be included in comparisons of clinical cohorts managed in different ways. It is therefore important to be able to give a rating to everyone if necessary. The approach suggested here is to rate such people on their current functional status and to indicate the existence of preinjury disability by putting a "*" beside the rating. These ratings can then be interpreted as meaning "still disabled at this level" or "disability no worse than this level" and dealt with appropriately in analysis. The circumstance in which we specifically suggest that cases are treated in this way is as follows. If the patient was not fully independent before injury, then they should be rated Severely Disabiled* (SD*) (or upper or lower SD* on the GOSE depending on the degree of preinjury disability). Depending on the purpose of the study, this approach could be extended by collecting more detailed information concerning the nature and level of preinjury disability.

In addition to the overall rating, the form gives a permanent record of current problem areas and prior limitations. This information serves as a source for audit of the data and can also be coded and used in analysis of outcome. The responses can be recorded as numerals in the boxes to aid computer coding (it is not intended that these digits should be added up). It should be borne in mind that responses to individual items may have lower reliability than the overall rating.

Definition of terms and notes to individual questions are given in the Appendix. The information given is deliberately detailed to allow the scales to be used by the nonspecialist.

Reliability

Patients. Fifty patients (eight female) were recruited from head injury admissions to the regional neurosurgi-

TABLE 1. DISTRIBUTIONS OF GOS RATINGS MADE BY A PSYCHOLOGIST AND RESEARCH NURSE FOR 50 HEAD-INJURED PATIENTS

Nurse / *Psychologist*	*Severe disability*	*Moderate disability*	*Good recovery*	
Severe disability	**18**	0	0	36%
Moderate disability	1	**11**	0	24%
Good recovery	1	2	**17**	40%
	40%	26%	34%	

cal unit. The patients were aged 18–76 years of age at the time of injury (mean = 39.4; SD = 16.5). Classification of severity of injury by worst recorded GCS indicated that 30% were severely injured (GCS 3–8), 14% had moderate injuries (GCS 9–12), and 56% were mild (GCS 13–15). The study was restricted to conscious survivors.

Procedure. Patients were interviewed 5–17 months postinjury (mean = 10.2 months; SD = 3.9). In 36 cases, the patient was interviewed alone, and in 14 the patient was seen together with a caregiver, relative, or friend. The outcome category was independently assigned by a research psychologist and either one of two research nurses. Interviews were carried out face to face on the same day. Raters carried out a structured interview using the GOSE questionnaire and used the information to assign outcomes on both eight-point and five-point scales.

Results. Preinjury limitations were reported in the following areas (number of cases in brackets): independence in home (1); shopping (1); work (17); social and leisure activities (2); family and friendships (6); other complaints (4). Two cases were rated as upper SD*, and these were treated as upper SD in the analysis. Distributions of ratings for the GOS and GOSE are shown in Tables 1 and 2. Overall agreement between raters was 92% for the GOS and 78% for the GOSE. As can be seen from Table 1, there were four cases in which there was disagreement between raters on the GOS, and in one case there was a disagreement of two categories. Review of these cases indicated that in three instances the respondent had given different information to the interviewers, and in one case the interviewer had misinterpreted a question. The patient with the largest disagreement had a history of alcoholism and was suffering from a wasting disease of the spine; he told one interviewer that he needed assistance for daily activities and did not like being away from home; however, he told the second interviewer that he went out six or seven times per week. The weighted kappa statistic was computed for observations between raters; this statistic takes into account the seriousness of disagreement between raters (Brennan & Silman, 1992). For the five-point scale κ_w was 0.89 and for the eight-point scale κ_w was 0.85.

CONCLUSION

The proposed structured interviews achieve a systematic subdivision of patients into outcome categories and have satisfactory interrater reliability. The kappa values for both the GOS and GOSE are regarded as "very good" (Brennan and Silman, 1992). Overall levels of interrater agreement in the present study compare favorably with previous reports (Anderson et al., 1993; Jennett et al., 1981; Maas et al., 1983): for example, Maas et al. (1983) report kappa values of 0.77 for the five-point scale and 0.48 for the eight-point scale in a "live" situation. Improved reliability does not completely eliminate limitations such as the use of broad social roles to define outcome categories, the reliance on verbal report, and the need for the exercise of some judgement by the interviewer. Nevertheless, the advantages of the GOS remain its simplicity, wide recognition, and the fact that differ-

TABLE 2. DISTRIBUTIONS OF GOS RATINGS MADE BY A PSYCHOLOGIST AND RESEARCH NURSE FOR 50 HEAD-INJURED PATIENTS

Nurse / *Psychologist*	*Severe disability*		*Moderate disability*		*Good recovery*		
	Lower	*Upper*	*Lower*	*Upper*	*Lower*	*Upper*	
Severe disability							
Lower	**8**						16%
Upper	3	**7**					20%
Moderate disability							
Lower		1	**7**	1			18%
Upper				**3**			6%
Good recovery							
Lower		1	2		**9**	2	28%
Upper					1	**5**	12%
	22%	18%	18%	8%	20%	14%	

ences in disability are clinically meaningful. Provided that the purpose and limits, as well as the benefits, of the GOS are appreciated, it can continue to have a central place in the assessment of head injury outcome.

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APPENDIX: Notes to Questions and Definition of Terms

Q1. Vegetative State

The definition of the vegetative state given in Q1 follows that given by Jennett et al. (1981). The Royal College of Physicians have published guidelines for deciding whether a patient is in a persistent vegetative state, and the simple approach suggested here is not intended to replace these guidelines in the management of the individual patient. If the patient is unable to obey commands or say words for some other reason, for example, because they are severely demented, then they are not in the vegetative state. "Any words" includes repetition of a simple word such as "No." A person able to communicate using a code would no longer be in the vegetative state.

Q2. Independence in the Home

Q2a. Dependency may be caused by physical impairment, but it is also often due to mental changes. People may require actual assistance with activities of daily living, they may need prompted or reminded to do things, or they may need someone with them to supervise them because they would be unsafe otherwise. In all these cases, they are dependent. However, many people receive assistance, but do not absolutely depend on it. This care or protection that is given by others should be distinguished from dependency: the person may well benefit from this help and may well have a real need for it, but such care does not mean that they are dependent in the sense required here.

A difficulty may arise if an activity was not normally carried out before the injury. For example, many men have little practical involvement in domestic matters and quite often will not usually prepare meals for themselves. In this case, it is sufficient that the person could, if the necessity arose, prepare food, even if this would be in a simple fashion.

Examples of minor domestic crises: what you do if . . . a glass gets dropped and broken, a tap is left running, a light goes out, it begins to get cold, a stranger comes to the door, . . . The person should be able to use the telephone to report problems or summon help.

Q2b (GOSE only). The patient is considered to be in the lower category of severe disability if they cannot be left alone for 8 h. This limit implies that a relative who is caring for them cannot work. If it is necessary to establish a time limit, it can be helpful to ask "what is the maximum amount of time they can be left alone?"

Q3. Shopping and Q4. Travel: Independence Outside the Home

Independence outside the home requires ability to plan, to take care of money, and behave appropriately in public. It must be established if the person is actually capable of carrying out these activities, rather than whether they do or not.

Q5. Work

Work is only used as an indicator of outcome if the person was working or actively seeking work before the injury, or if they were studying.

Q5a. "Work" refers to jobs that are paid at a reasonable rate and which, in principle at least, are open to others. "Reduced capacity for work"—Any of the following indicate reduced capacity for work: (a) change in level of skill or responsibility required; (b) change from full-time to part-time working; (c) special allowances made by employer (e.g., increased supervision at work); and (d) change from steady to casual employment (i.e., no longer able to hold steady job).

Note that sometimes change in employment status may be unrelated to head injury, e.g., due to end of contract, retirement, or redundancy. Such changes do not indicate a reduced capacity for work.

Students Q5a. If the person was a student before injury, then "study" can be substituted for "work." Students should be able to return to their previous course and not have noted adverse effects on their ability to study. If someone has been absent from college because of injury, then there may be some disruption caused by the absence itself, and this needs to be discounted when considering if the person has problems due to the head injury. Examples of problems which indicate reduced capacity for study: (a) increased difficulties in studying (e.g., needing to spend much more time than before); (b) unaccustomed problems with progress (e.g., failing examinations); and (c) revised program of study because of problems (e.g., studying for a lesser qualification).

Q5b (GOSE only). "Noncompetitive work" includes work done voluntarily, jobs that are specifically designated for disabled people, and work in sheltered workshops. Normally, ability to work is indicative of independence; however, occasionally, someone in the upper severe disability range may be working in a sheltered workshop.

Students, Q5b. (a) If the student has a reduced capacity for study but is still studying, then they are Upper Moderate disability; and (b) if the student is currently unable to study, then they are Lower Moderate disability.

Q6. Social and Leisure Activities

Social and leisure activities will vary depending on the age and background of the patient. Representative social and leisure activities reported by patients in Glasgow include the following: (a) participating in sport, e.g., football, swimming etc., (b) attending sporting events as a spectator, (c) going walking, (d) going to a club or pub, and (e) visiting friends.

Some leisure activities are seasonal, and one must be careful to exclude changes in activity that are simply due to this factor.

Typical problems that may interfere with social and leisure activities: lack of motivation or initiative, avoidance of social involvement, physical problems such as loss of mobility, cognitive problems such as poor concentration, and problems such as poor temper control or impatience.

Q6b. Extent of restriction. If it is necessary to question in detail, then ask the person how often they participated in social and leisure activities outside the home before the injury (i.e., how many occasions per week) and how often they participate now.

Measuring extent of participation is in terms of occasions per week emphasizes a quantifiable aspect of social and leisure activities. Sometimes, quality of participation is affected by the head injury; for example, the person may become a spectator in a sport rather than an active participant. However, changes such as this are very difficult to quantify and can reflect the specially demanding nature of some sports. Thus, for the sake of simplicity, it is the fact of participation that is rated in the interview. Experience suggests that the main effect of head injury on social and leisure activities tends to be withdrawal from activities that involve social interaction: the simple approach adopted here is sensitive to such changes.

Q6c. Participating regularly in social and leisure activities means participating in at least one activity outside the home each week.

Q7. Family and Friendships

The question is specifically aimed at alterations in relationships as a result of head injury. The presence of a reported change in personality is not of itself sufficient to warrant classifying the person as moderately disabled—the change must be having an adverse impact on family and friendships.

Q7b. Extent of disruption or strain. The following definitions apply: (a) Occasional—Some problems since injury, but less than once a week and not causing continuous strain. For example, occasional bad temper, but things blow over. (b) Frequent—Problems at least weekly, strain on relationships, but regarded as tolerable. For example, temper outbursts at least once a week resulting in modification of closeness of relationships. (c) Constant daily problems—Breakdown or threatened breakdown of relationship within family or friendship; problems regarded as intolerable. If a family have become very withdrawn and socially isolated as a result of injury, then this also represents constant disruption.

Q8 (GOSE Only). Return to Normal Life

Q8a. The list of problems here includes those described as the postconcussion syndrome. The problems are impairments; in order to cause disability, they must impinge on functioning in everyday life. Similar problems are reported in the general population: it is thus important to establish that the problems have developed since injury.

STRUCTURED INTERVIEWS FOR THE GOS AND GOSE

Glasgow Outcome Scale

Patient's name: _____ Date of interview: _____

Date of Birth: _____ Date of injury _____ Gender: M / F

Age at injury: _____ Interval post-injury: _____

Respondent: Patient alone ___ Relative/ friend/ carer alone ___ Patient + relative/ friend/ carer ___

Interviewer: _____

CONSCIOUSNESS

1. Is the head injured person able to obey simple commands, or say any words? ☐ 1 = No (VS) 2 = Yes

Anyone who shows ability to obey even simple commands, or utter any word or communicate specifically in any other way is no longer considered to be in the vegetative state. Eye movements are not reliable evidence of meaningful responsiveness. Corroborate with nursing staff. Confirmation of VS requires full assessment as in the Royal College of Physician Guidelines.

INDEPENDENCE IN THE HOME

2a Is the assistance of another person at home essential every day for some activities of daily living? ☐ 1 = No 2 = Yes (SD)

For a 'No' answer they should be able to look after themselves at home for 24 hours if necessary, though they need not actually look after themselves. Independence includes the ability to plan for and carry out the following activities: getting washed, putting on clean clothes without prompting, preparing food for themselves, dealing with callers, and handling minor domestic crises. The person should be able to carry out activities without needing prompting or reminding, and should be capable of being left alone overnight

2c Was assistance at home essential before the injury? ☐ 1=No 2=Yes

INDEPENDENCE OUTSIDE THE HOME

3a Are they able to shop without assistance? ☐ 1 = No (SD) 2 = Yes

This includes being able to plan what to buy, take care of money themselves, and behave appropriately in public. They need not normally shop, but must be able to do so.

3b Were they able to shop without assistance before the injury? ☐ 1=No 2=Yes

4a Are they able to travel locally without assistance? ☐ 1 = No (SD) 2 = Yes

They may drive or use public transport to get around. Ability to use a taxi is sufficient, provided the person can phone for it themselves and instruct the driver.

4b Were they able to travel without assistance before the injury? ☐ 1=No 2=Yes

WORK

5a Are they currently able to work to their previous capacity? ☐ 1 = No (MD) 2 = Yes (GR)

If they were working before, then their current capacity for work should be at the same level. If they were seeking work before, then the injury should not have adversely affected their chances of obtaining work or the level of work for which they are eligible. If the patient was a student before injury then their capacity for study should not have been adversely affected.

5b Were they either working or seeking employment before the injury (answer yes) or were they doing neither (answer no)? ☐ 1=No 2=Yes

SOCIAL & LEISURE ACTIVITIES

6a Are they able to resume regular social and leisure activities outside home? ☐ 1 = No - Go to 6b 2 = Yes (GR)

They need not have resumed all their previous leisure activities, but should not be prevented by physical or mental impairment. If they have stopped the majority of activities because of loss of interest or motivation then this is also considered a disability.

6b What is the extent of restriction on their social and leisure activities?
a) Participate a bit less: at least half as often as before injury.
b) Participate much less or unable to participate ☐ 1 = a (GR) 2 = b (MD)

6c Did they engage in regular social and leisure activities outside home before the injury? ☐ 1=No 2=Yes

FAMILY & FRIENDSHIPS

7a Have there been psychological problems which have resulted in ongoing family disruption or disruption to friendships? ☐ 1 = No (GR) 2 = Yes - Go to 7b

Typical post-traumatic personality changes: quick temper, irritability, anxiety, insensitivity to others, mood swings, depression, and unreasonable or childish behaviour.

7b What has been the extent of disruption or strain?
a) Occasional - less than weekly
b) Frequent or constant - once a week or more ☐ 1 = a (GR) 2 = b (MD)

7c. Were there problems with family or friends before the injury? ☐ 1=No 2=Yes

If there were problems before injury, but these have become markedly worse since injury, then answer "No" to Q7c.

Epilepsy:
Since the injury has the head injured person had any epileptic fits? No / Yes
Have they been told that they are currently at risk of developing epilepsy? No / Yes

What is the most important factor in outcome?
Effects of head injury ___ Effects of illness or injury to another part of the body ___ A mixture of these ___

Scoring: The patient's overall rating is based on the lowest outcome category indicated on the scale. Refer to Guidelines for further information concerning administration and scoring.

1	Dead	☐
2	Vegetative State (VS)	
3	Severe Disability (SD)	
4	Moderate Disability (MD)	
5	Good Recovery (GR)	

Glasgow Outcome Scale - Extended

Patient's name: _____ Date of interview: _____

Date of Birth: _____ Date of injury _____ Gender: M / F

Age at injury: _____ Interval post-injury: _____

Respondent: Patient alone ___ Relative/ friend/ carer alone ___ Patient + relative/ friend/ carer ___

Interviewer: _____

CONSCIOUSNESS

1. Is the head injured person able to obey simple commands, or say any words? ☐ 1 = No (VS) 2 = Yes

Anyone who shows ability to obey even simple commands, or utter any word or communicate specifically in any other way is no longer considered to be in the vegetative state. Eye movements are not reliable evidence of meaningful responsiveness. Corroborate with nursing staff. Confirmation of VS requires full assessment as in the Royal College of Physician Guidelines.

INDEPENDENCE IN THE HOME

2a Is the assistance of another person at home essential every day for some activities of daily living? ☐ 1 = No 2 = Yes

For a 'No' answer they should be able to look after themselves at home for 24 hours if necessary, though they need not actually look after themselves. Independence includes the ability to plan for and carry out the following activities: getting washed, putting on clean clothes without prompting, preparing food for themselves, dealing with callers, and handling minor domestic crises. The person should be able to carry out activities without needing prompting or reminding, and should be capable of being left alone overnight.

2b Do they need frequent help or someone to be around at home most of the time? ☐ 1 = No (Upper SD) 2 = Yes (Lower SD)

For a 'No' answer they should be able to look after themselves at home for up to 8 hours during the day if necessary, though they need not actually look after themselves.

2c Was assistance at home essential before the injury? ☐ 1=No 2=Yes

INDEPENDENCE OUTSIDE THE HOME

3a Are they able to shop without assistance? ☐ 1 = No (Upper SD) 2 = Yes

This includes being able to plan what to buy, take care of money themselves, and behave appropriately in public. They need not normally shop, but must be able to do so.

3b Were they able to ship without assistance before the injury? ☐ 1=No 2=Yes

4a Are they able to travel locally without assistance? ☐ 1 = No (Upper SD) 2 = Yes

They may drive or use public transport to get around. Ability to use a taxi is sufficient, provided the person can phone for it themselves and instruct the driver.

4b Were they able to travel without assistance before the injury? ☐ 1=No 2=Yes

WORK

5a Are they currently able to work to their previous capacity? ☐ 1 = No 2 = Yes

If they were working before, then their current capacity for work should be at the same level. If they were seeking work before, then the injury should not have adversely affected their chances of obtaining work or the level of work for which they are eligible. If the patient was a student before injury then their capacity for study should not have been adversely affected.

5b How restricted are they?
a) Reduced work capacity.
b) Able to work only in a sheltered workshop or non-competitive job, or currently unable to work. ☐ 1 = a (Upper MD) 2 = b (Lower MD)

5b Were they either working or seeking employment before the injury (answer yes) or were they doing neither (answer no)? ☐ 1=No 2=Yes

SOCIAL & LEISURE ACTIVITIES

6a Are they able to resume regular social and leisure activities outside home? ☐ 1 = No 2 = Yes

They need not have resumed all their previous leisure activities, but should not be prevented by physical or mental impairment. If they have stopped the majority of activities because of loss of interest or motivation then this is also considered a disability.

6b What is the extent of restriction on their social and leisure activities?
a) Participate a bit less: at least half as often as before injury.
b) Participate much less: less than half as often.
c) Unable to participate: rarely, if ever, take part. ☐ 1 = a (Lower GR) 2 = b (Upper MD) 3 = c (Lower MD)

6c Did they engage in regular social and leisure activities outside home before the injury? ☐ 1=No 2=Yes

FAMILY & FRIENDSHIPS

7a Have there been psychological problems which have resulted in ongoing family disruption or disruption to friendships? ☐ 1 = No 2 = Yes

Typical post-traumatic personality changes: quick temper, irritability, anxiety, insensitivity to others, mood swings, depression, and unreasonable or childish behaviour.

7b What has been the extent of disruption or strain?
a) Occasional - less than weekly
b) Frequent - once a week or more, but tolerable.
c) Constant - daily and intolerable. ☐ 1 = a (Lower GR) 2 = b (Upper MD) 3 = c (Lower MD)

7c. Were there problems with family or friends before the injury? ☐ 1=No 2=Yes

If there were problems before injury, but these have become markedly worse since injury, then answer "No" to Q7c.

RETURN TO NORMAL LIFE

8a Are there any other current problems relating to the injury which affect daily life? ☐ 1 = No (Upper GR) 2 = Yes (Lower GR)

Other typical problems reported after head injury: headaches, dizziness, tiredness, sensitivity to noise or light, slowness, memory failures, and concentration problems.

8b Were similar problems present before the injury? ☐ 1=No 2=Yes

If there were some problems before injury but these have become markedly worse since injury, then answer No to Q8b

STRUCTURED INTERVIEWS FOR THE GOS AND GOSE

Epilepsy:
Since the injury has the head injured person had any epileptic fits? No / Yes
Have they been told that they are currently at risk of developing epilepsy? No / Yes

What is the most important factor in outcome?
Effects of head injury ___ Effects of illness or injury to another part of the body ___ A mixture of these ___

Scoring: The patient's overall rating is based on the lowest outcome category indicated on the scale. Refer to Guidelines for further information concerning administration and scoring

1	Dead
2	Vegetative State (VS)
3	Lower Severe Disability (Lower SD)
4	Upper Severe Disability (Upper SD)
5	Lower Moderate Disability (Lower MD)
6	Upper Moderate Disability (Upper MD)
7	Lower Good Recovery (Lower GR)
8	Upper Good Recovery (Upper GR)

Appendix C

Follow-up Survey Incorporating GOSE and DRS

Resuscitation Outcomes Consortium

Complete this form for:
-all TBI patients (at discharge, at one month post discharge if patient difficult to contact and at 6 months post-injury)

ROC
Hypertonic Saline Protocol

TBI Outcome Interview

Version 1.00.00
Date: 06/30/2006

Date *(mm/dd/yyyy)* ___ / ___ / ___

Time call received at dispatch*(24hr clock)*
___ : ___ : ___ *(hh:mm:ss)* ○ **Estimated** ○ **From dispatch**

HS ID: ___ - ___ - ___

Site Linking ID *(optional)*

Incident Number*(optional)*

1. Interview

Date: ___ / ___ / ___ *(mm/dd/yyyy)*

Interviewer: _____ *(30)*

Interval post injury: _____

2. Respondent:

○ Patient alone
○ Caregiver alone
○ Patient & Caregiver
→ Identify caregiver: ○ Relative ○ Friend ○ Professional (RN, employed caregiver)

Was patient able to answer these questions?

Yes	No	
○	○	(1)"Can you tell me what you will be asked to do as a participant in this study?"
○	○	(2)"Can you tell me what you can do if you no longer wish to participate in the study?"

GOSE Section

3. Consciousness:

a. Is the head injured person able to obey simple commands or say any words?

(Anyone who shows ability to obey even simple commands, or utter any words or communicate specifically in any other way is no longer considered to be in a vegetative state. Eye movements are not reliable evidence of meaningful responsiveness. If unclear, corroborate with nursing staff.)

○ Yes
○ No

4. Independence in the home:

a. Is the assistance of another person at home essential every day for some activities of daily living?

(For a No, the patient should be able to care for himself at home for 24 hours if necessary. Independence include the ability to plan for and carry out the following activities: bathing, dressing, preparing food, dealing with callers, and handling minor domestic crises. The person should be able to carry out these activities without prompting or reminding and should be capable of being left alone overnight.)

○ Yes
○ No

b. Does the patient require frequent help or someone to be around the home most of the time?

(For a No, the patient should be able to care for himself for up to 8 hours a day if necessary.)

○ Yes
○ No

c. Was assistance at home required before the injury?

○ Yes
○ No

continue to page 2

ROC Hypertonic Saline Protocol

TBI Outcome Interview

Date *(mm/dd/yyyy)* ___/___/____

Time call received at dispatch*(24hr clock)*
___:___:___ *(hh:mm:ss)* ○ **Estimated** ○ **From dispatch**

HS ID: ___-___-___

Site Linking ID *(optional)* _____

Incident Number*(optional)* _____

5. Independence outside the home

a. Shopping:

(This includes being able to plan what to buy, take care of money independently and behave appropriately in public.)

i. Can the patient shop without assistance?

○ Yes
○ No

ii. Was the patient able to shop without assistance prior to the injury?

○ Yes
○ No

b. Travel:

(This includes either driving or use of public transit. Ability to use a taxi is sufficient, provided the person can call for the taxi and instruct the driver independently.)

i. Is the patient able to travel locally without assistance?

○ Yes
○ No

ii. Was the patient able to travel without assistance prior to the injury?

○ Yes
○ No

c. Work:

(If patients were working before, then their current capacity for work should be at the same level. If they were seeking work before, then the injury should not have adversely affected their chance of obtaining work at the level to which they were eligible. If the patient was a student before the injury, then their capacity for study should not have been adversely affected.)

i. Is the patient working at his/her previous capacity?

○ Yes
○ No

ii. How restricted are they?

○ Reduced work capacity
○ Able to work only in a sheltered workshop or non-competitive job, or unable to work
○ Unable to work at all

iii. Prior to injury was the patient?

○ Working full-time, list occupation: _____ *(30)*
○ Working part-time, list occupation: _____ *(30)*
○ Seeking employment
○ Student, level of education: _____ *(30)*
○ Unable to work

continue to page 3

ROC Hypertonic Saline Protocol

TBI Outcome Interview

Date *(mm/dd/yyyy)* ___/___/___

Time call received at dispatch*(24hr clock)* ___:___:___ *(hh:mm:ss)* ○ **Estimated** ○ **From dispatch**

HS ID: ___-___-___

Site Linking ID *(optional)* _____

Incident Number*(optional)* _____

6. Social & Leisure activities:

(They need not have resumed all their previous leisure activities, but should not be prevented by physical or mental impairment. If they have stopped the majority of activities because of loss of interest or motivation then this is also considered a disability.)

a. Is the patient able to resume regular social and leisure activities outside the home?

○ Yes
○ No

b. What is the extent of restriction on their social and leisure activities?

○ Participate a bit less *(at least half as often as before injury)*
○ Participate much less *(less than half as often)*
○ Unable to participate *(rarely, if ever, take apart)*

c. Did the patient engage in regular social and leisure activities outside the home before the injury?

○ Yes
○ No

7. Family & Friendships:

(Typical post-traumatic personality changes: quick temper, irritability, anxiety, insensitivity to others, mood swings, depression, and unreasonable childish behavior.)

a. Have there been psychological problems which have resulted in ongoing family disruption or disruption to friendships?

○ Yes
○ No

b. What has been the extent of the disruption or strain?

○ Occasional *(less than weekly)*
○ Frequent *(once a week or more, but tolerable)*
○ Constant *(daily and intolerable)*

c. Were there problems with family or friends before the injury?

(If there were some problems, but the problems have become markedly worse since the injury then the answer should be NO)

○ Yes
○ No

8. Return to normal life:

(Other typical problems reported after head injury include: headaches, dizziness, tiredness, sensitivity to noise/light, slowness, memory failures, and concentration problems.)

a. Are there any other current problems relating to the injury that affect daily life?

○ Yes
○ No

b. Were there similar problems present before the injury?

○ Yes
○ No

continue to page 4

ROC Hypertonic Saline Protocol

TBI Outcome Interview

Date *(mm/dd/yyyy)* ___ / ___ / ___

Time call received at dispatch*(24hr clock)* ___ : ___ : ___ *(hh:mm:ss)* ○ **Estimated** ○ **From dispatch**

HS ID: ___ - ___ - ___

Site Linking ID *(optional)* ___

Incident Number*(optional)* ___

9. What do you feel has had the greatest impact on outcome following this injury?

- ○ Effects of the head injury
- ○ Effects of the injury to another part of the body
- ○ A combination of these

DRS Section

10. Level of consciousness:

a. Does the patient open eyes?

- ○ Spontaneously
- ○ To speech
- ○ To pain
- ○ None

b. Is the patient's speech?

- ○ Oriented
- ○ Confused but conversant
- ○ Inappropriate words
- ○ Incomprehensible
- ○ None

c. What is the patient's best motor response?

- ○ Obeys commands
- ○ Localizes to pain
- ○ Withdraws from pain
- ○ Flexor posturing
- ○ Extensor posturing
- ○ None

11. Independence and cognition:

Note: 11a, 11b, 11c focus specifically on cognitive ability, not physical ability, to perform these tasks

a. Does the patient have the cognitive ability to feed himself?

- ○ Complete
- ○ Partial
- ○ Minimal
- ○ None

b. Does the patient have the cognitive ability to use the toilet?

- ○ Complete
- ○ Partial
- ○ Minimal
- ○ None

continue to page 5

ROC Hypertonic Saline Protocol

TBI Outcome Interview

Date *(mm/dd/yyyy)* ___ / ___ / ___

Time call received at dispatch*(24hr clock)*
___ : ___ : ___ *(hh:mm:ss)* ○ **Estimated** ○ **From dispatch**

HS ID: ___ - ___ - ___

Site Linking ID *(optional)*

Incident Number*(optional)*

continued from page 4 Item 11

c. Does the patient have the cognitive ability to groom and dress?

- ○ Complete
- ○ Partial
- ○ Minimal
- ○ None

d. Would you describe the patient as currently?

- ○ Completely independent
- ○ Independent in a special environment
- ○ Mildly dependent *(needs limited assistance, non-resident helper)*
- ○ Moderately dependent *(needs person in home for some assistance)*
- ○ Markedly dependent *(needs assistance with all activities at all times)*
- ○ Totally dependent *(24-hour nursing care required)*

12. GOS: ___ **GOS-E:** ___ **DRS:** ___

Scoring

GOS: The overall rating is based on the lowest outcome category indicated:

1. Dead
2. Vegetative state (VS)
3. Severe disability (SD)
4. Moderate disability (MD)
5. Good recovery (GR)

GOS-extended: The overall rating is based on the lowest outcome category indicated:

1. Dead
2. Vegetative state (VS)
3. Lower severe disability (Lower SD)
4. Upper severe disability (Upper SD)
5. Lower moderate disability (Lower MD)
6. Upper moderate disability (Upper MD)
7. Lower good recovery (Lower GR)
8. Upper good recovery (Upper GR)

DRS: Score is based upon point total

# points	Level of disability
0	None
1	Mild
2-3	Partial
4-6	Moderate
7-11	Moderately severe
12-16	Severe
17-21	Extremely severe
22-24	Vegetative state
25-29	Extreme vegetative state
30	Death

Person responsible for data on this form: ___

Appendix D

DRS (Disability Rating Score)

Patient Name_____

Rater_____

Date Completed_____

Disability Rating Scale (DRS)

Arousability, Awareness, & Responsivity

Eye Opening
- ❑ 0 Spontaneous
- ❑ 1 To Speech
- ❑ 2 To Pain
- ❑ 3 None

Communication Ability
- ❑ 0 Oriented
- ❑ 1 Confused
- ❑ 2 Inappropriate
- ❑ 3 Incomprehensible
- ❑ 4 None

Motor Response
- ❑ 0 Obeying
- ❑ 1 Localizing
- ❑ 2 Withdrawing
- ❑ 3 Flexing
- ❑ 4 Extending
- ❑ 5 None

Cognitive Ability for Self Care Activities

Knows how and when to feed, toilet or groom self

Feeding
- ❑ 0.0 Complete
- ❑ 0.5
- ❑ 1.0 Partial
- ❑ 1.5
- ❑ 2.0 Minimal
- ❑ 2.5
- ❑ 3.0 None

Toileting
- ❑ 0.0 Complete
- ❑ 0.5
- ❑ 1.0 Partial
- ❑ 1.5
- ❑ 2.0 Minimal
- ❑ 2.5
- ❑ 3.0 None

Grooming
- ❑ 0.0 Complete
- ❑ 0.5
- ❑ 1.0 Partial
- ❑ 1.5
- ❑ 2.0 Minimal
- ❑ 2.5
- ❑ 3.0 None

Dependence on Others

Level of Functioning

Physical & cognitive disability

- ❑ 0.0 Completely Independent
- ❑ 0.5
- ❑ 1.0 Independent in special environment
- ❑ 1.5
- ❑ 2.0 Mildly Dependent-Limited assistance
  Non-resident helper
- ❑ 2.5
- ❑ 3.0 Moderately Dependent-moderate assist
  Person in home
- ❑ 3.5
- ❑ 4.0 Markedly Dependent
  Assistance with all major activities, all times
- ❑ 4.5
- ❑ 5.0 Totally Dependent
  24 hour nursing care

Psychosocial Adaptability

Employability

As full time worker, homemaker, student

- ❑ 0.0 Not Restricted
- ❑ 0.5
- ❑ 1.0 Selected jobs, competitive
- ❑ 1.5
- ❑ 2.0 Sheltered workshop, Noncompet.
- ❑ 2.5
- ❑ 3.0 Not Employable

Total Score (sum all scores) _____

Appendix E

Follow-up Contact Information Form

Complete this form:
-For all patients that were discharged alive from the hospital
-Retain at site; do not enter on web

ROC
Hypertonic Saline Protocol

Patient/Family information

Date of episode: ☐☐ / ☐☐ / ☐☐☐☐ (mm/dd/yyyy)

Time call received at dispatch (24hr clock): ☐☐ : ☐☐ : ☐☐ (hh:mm:ss)

Episode ID: ☐☐☐ - ☐☐☐☐ - ☐☐

1) Date Completed:

☐☐ / ☐☐ / ☐☐☐☐ (mm/dd/yyyy)

2) Patient contact information :

Name: _____

Permanent address: _____

_____

City: _____ State/Prov: _____ Zip: _____

Telephone: ( ) _____ ( ) _____ ( ) _____
Home *Work* *Other*

3) Patient discharge information:

a. Patient was discharged to:

- ○ Home
- ○ Rehabilitation
- ○ Nursing home
- ○ Family member's home
- ○ Other: _____

b. Name of contact/head of household : _____

c. Relation:

- ○ Staff (Rehab, Nursing home)
- ○ Caregiver
- ○ Family member
- ○ Other: _____

d. Address and phone :

Address: _____

_____

City: _____ State/Prov: _____ Zip: _____

Telephone: ( ) _____ ( ) _____
Home *Alternate*

4) Employer contact information:

Patient: ○ Not Applicable ○ Not Available
Employer name:
Address:
City:
State/Prov: Zip:
Telephone: ( )

Spouse: ○ Not Applicable ○ Not Available
Employer name:
Address:
City:
State/Prov: Zip:
Telephone: ( )

(continue on to page 2)

Date of episode: ___ / ___ / ___ (mm/dd/yyyy)

Time call received at dispatch (24hr clock): ___ : ___ : ___ (hh:mm:ss)

Episode ID: ___ - ___ - ___

5) Personal physician (primary care) contact information:

Name: _____

Clinic name: _____

Permanent address: _____

_____

City: _____ State/Prov: _____ Zip: _____

Telephone: ( ) _____

6) Name of another person (not living with patient) who would be likely to know of his/her whereabouts:

Name: _____

Address: _____

_____

City: _____ State/Prov: _____ Zip: _____

Telephone: ( ) _____ ( ) _____ ( ) _____

Home *Work* *Other*

Relationship to patient: _____

7) Other notes and comments that might assist in contacting or locating the patient:

_____

_____

_____

_____

_____

_____

_____

_____

Name of person responsible for data on this form:

Name: _____

(end of form)

Patient Information Form

The purpose of this form is to provide the information necessary to contact the subject or the subject's representative who have consented for follow-up.

Follow-up schedule:

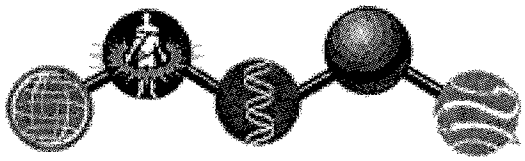
- **Day 28 - All subjects** who have left the hospital prior to Day 28 will get a follow-up call to assess vital status and complications since discharge (See the form "Follow-up 28 days"). TBI subjects should have their contact information validated at this time.
- **TBI subjects <u>ONLY</u>** will be contacted additionally at:
    1) **one month after *discharge*** to both administer the TBI Outcome interview and confirm contact information.
    2) **six months after *injury*** to administer the TBI outcome Interview for the final time.

Previous experience with follow-up studies in the trauma population has demonstrated variable success in achieving adequate response rates. This is a relatively young and mobile population and thus can be difficult to track once discharged from the hospital.

In the event that the patient changes his location of residence from the time of discharge, it is paramount that there are alternative names, addresses, and phone numbers that can be used to contact the patient or the patient's representatives. It may be necessary to contact the patient's family (or friends) at the time of discharge in order to complete the entire form. This contact information is vital in order to ensure adequate follow-up data for vital statistics and basic neurologic function. This form will be kept at the site.

Appendix F

Management Guidelines



INFLAMMATION
& the Host Response to Injury

TR1: Clinical Protocol for Trauma Resuscitation

The contents of this protocol were developed by the Inflammation and the Host Response to Injury Large-Scale Collaborative Research Program under a grant from the National Institute of General Medical Sciences. If any material from this protocol is used, proper credit to the Program and the NIGMS must be given.

Summary

The goal of this protocol is to guide consistent resuscitation efforts. Developed by expert consensus, this protocol progresses through a tiered approach to resuscitation, beginning with the widely accepted Advanced Trauma Life Support protocol. Since the majority of severe trauma patients present in shock due to excessive hemorrhaging, these patients require crystalloid administration and blood transfusion. The protocol aims for an optimal hematocrit of 30 during the acute resuscitation phase. If volume repletion efforts are inadequate to restore hemodynamic stability and hypovolemia is considered unlikely, a pulmonary artery catheter and/or echocardiogram may help rule out cardiac dysfunction as the etiology. Data from the pulmonary artery catheter are used to maintain an adequate, but not supranormal, cardiac index and oxygen delivery.

Protocol Goals

· Early recognition of the shock state for prompt initiation of resuscitation
· Insure acute resuscitation of the trauma patient is conducted in a consistent manner
· Provide guidelines for the use of a pulmonary artery catheter (PAC) in the resuscitation of the major trauma patient

Protocol Rationale

The primary objective of this protocol is to guide consistent resuscitation efforts

for all eligible.1,2 There is no Level I research evidence on how to best resuscitate the severely injured trauma patient nor are there resuscitation parameters whose close monitoring (to guide intervention) clearly impact on patient outcome.3-5 Further, the proof of benefit of a pulmonary artery catheter to guide resuscitation in a population of young, previously healthy subjects is limited.3 Given the lack of available evidence, this protocol has been developed by expert consensus to promote a tiered approach to trauma resuscitation. The protocol begins with the widely accepted Advanced Trauma Life Support (ATLS) protocol and continues with the ATLS protocol until it becomes evident the patient is at high risk for post-traumatic organ failure, by virtue of an anticipated need for blood transfusion in the clinical context of either ongoing shock or evidence of impaired tissue perfusion (base deficit $^{3}6$).6

Once a high-risk patient is identified, the patient should have a central venous pressure monitor placed in the subclavian or internal jugular position. If the central venous pressure (CVP) is high (CVP >15) an echocardiogram and early insertion of a pulmonary artery catheter should be considered to rule out tamponade or cardiac dysfunction and to better guide resuscitation.

While the majority of severe trauma patients present in shock due to excessive hemorrhaging, the optimal hematocrit required to lower the risk of organ failure in patients with hemorrhagic shock is unknown, yet the risks of inadequate blood transfusion given the potential for ongoing blood loss are significant. As a result of compromise, the protocol aims for a minimum hematocrit of 30 during the acute resuscitation phase.

The protocol calls for volume repletion to a central venous pressure of 10-15 in the presence of sustained tachycardia and/or hypotension. If intravascular volume has been appropriately increased to this level and the patient remains unstable or has a persistent base deficit, there exists a component of cardiac dysfunction. At this point, a pulmonary artery catheter may be helpful to evaluate cardiac dysfunction.

Once data from the pulmonary artery catheter are available, the principal objective is to maintain an adequate (not supranormal) cardiac index (CI) of 3.8 l/ min/m2. There is little evidence to support supranormal resuscitation goals in this cohort of patients. Given a hemoglobin (Hgb) of 10 g/dl and a reasonable oxygen saturation (SaO2 >90%), this should provide an oxygen delivery of over 450 ml/ min/m2. Cardiac index is supported first through an increase in preload to a pulmonary capillary wedge pressure (PCWP) of at least 15, with an incremental increase to a PCWP no higher than 25 through repeated administration of intravascular volume boluses to achieve this endpoint (Starling curve). If there is no further increase in CI with repeated administration of fluid, then further administration of fluid to increase the PCWP is unwarranted. If the goal CI has not been attained, inotropic support should be strongly considered. In the presence of hypotension, consider the use of dopamine, norepinephrine, or epinephrine and continually re-assess for ongoing bleeding or hypovolemia. Without hypotension, dobutamine (or milrinone) should be selected at the discretion of the attending physician.

Occasionally, there are circumstances where there is persistent hypotension despite an adequate cardiac output. Continued re-evaluation for bleeding and/or hypovolemia is indicated. Once addressed, an agent with vasopressor properties should be considered. The specific choice of agent (norepinephrine, vasopressin, or dopamine) is at the discretion of the attending physician.

Protocol Details

1. Begin resuscitation using the standard ATLS protocol.

2. Identify the high risk patient:
· Anticipated need for blood transfusion AND
· Continued base deficit ³6 OR systolic blood pressure <90 mm Hg

3. Insert central venous pressure monitor in the subclavian or internal jugular vein.

4. If sustained heart rate (HR) >120 or systolic blood pressure (SBP) <90, administer blood and crystalloid to Hgb of 10 and CVP of 15 until HR <120 or SBP >90.

5. If sustained HR >120 or SBP <90 and CVP ³15, consider cardiac dysfunction or tamponade and insert a pulmonary artery catheter (PAC) and consider pericardial ultrasound or echocardiogram.

6. Insert a PAC if there is no improvement in base deficit despite administration of blood and crystalloid to Hgb of 10 and CVP of 10-15.

7. Once a PAC is inserted, aim for CI ³3.8
· If CI <3.8 and PCWP <15, administer crystalloid to PCWP =15
· If CI <3.8 and PCWP >15 and PCWP <25, administer 500 cc crystalloid (or blood as appropriate) boluses with repeat measurement of CI and PCWP within 5 minutes after each bolus (Starling curve)
o If CI drops by ³0.3, record prior PCWP as "optimal" and maintain this PCWP with crystalloid (and/or blood to maintain Hgb ³10)
o If CI <3.8 and optimal PCWP has been attained (or PCWP ³25), begin inotrope of choice to achieve CI >3.8; consider echocardiogram
· If CI <3.8 with MAP £60, re-evaluate for bleeding and/or hypovolemia, then treat with an inotrope with vasopressor effects (e.g. dopamine, levophed or epinephrine)
· If CI ³3.8 with MAP £60, then treat with a vasopressor (e.g. levophed or vasopressin)

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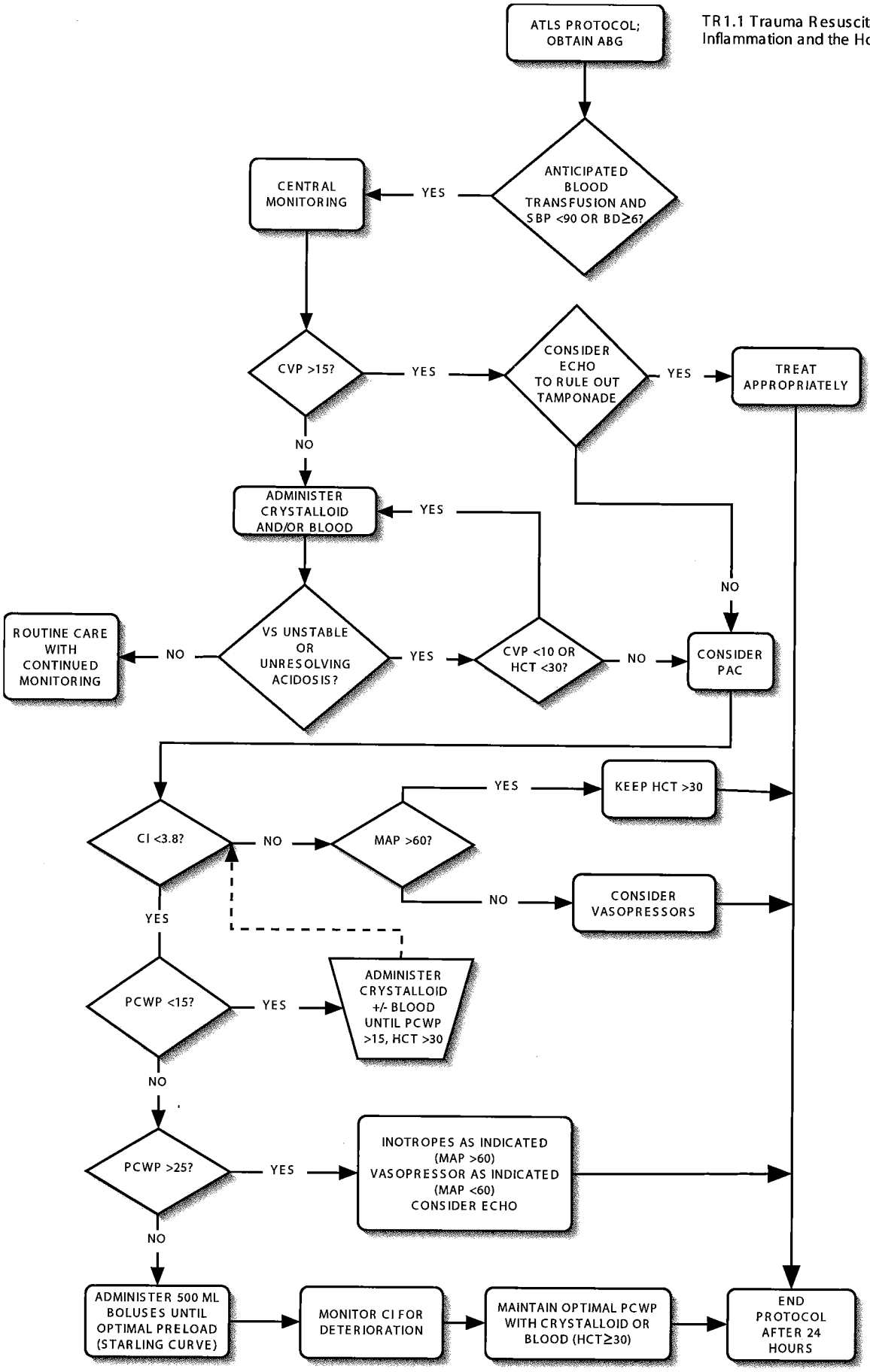
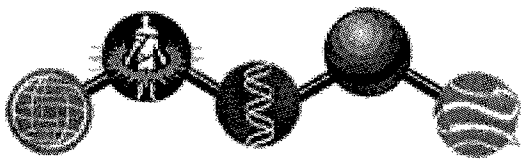
Accompanying Document

TR1.1 Trauma Resuscitation Flowchart

Published on www.gluegrant.org in May 2004 by the Inflammation and the Host Response to Injury Investigators.
Supported by a Large-Scale Collaborative Project Award (U54-GM62119) from The National Institute of General Medical Sciences.

TR1.1 Trauma Resuscitation Flowchart
Inflammation and the Host Response to Injury





INFLAMMATION
& the Host Response to Injury

TR2: Clinical Protocol for Mechanical Ventilation

The contents of this protocol were developed by the Inflammation and the Host Response to Injury Large-Scale Collaborative Research Program under a grant from the National Institute of General Medical Sciences. If any material from this protocol is used, proper credit to the Program and the NIGMS must be given.

Summary

This protocol promotes a low tidal volume, lung-protective strategy for ventilating patients meeting the criteria for acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). To achieve adequate oxygenation, variable positive end-expiratory pressure (PEEP) and inspired oxygen (FiO2) is left to physician discretion, but the FiO2 to PEEP ratio should be less than or equal to 5. If arterial oxygenation is not within the target range, then either FiO2 or PEEP should be adjusted within 30 minutes, after which oxygenation should be reassessed within 15 minutes and subsequent adjustments made if necessary. The mode of mechanical ventilation is left to physician discretion; however, once patients are ready to wean, a daily trial of spontaneous breathing offers the best chances for early extubation. If the patient cannot be weaned from mechanical ventilation, the protocol recommends gradual reduction in breathing support, at the physician's discretion. In these patients, subsequent cycles of spontaneous breathing, weaning, and breathing support overnight for rest should be continued daily until the patient is breathing independently.

Protocol Goals

· Insure that a low tidal volume, lung protective strategy is used for the ventilation of subjects who meet criteria for acute lung injury (ALI) or acute respiratory distress syndrome (ARDS)
· Provide guidelines for the use of PEEP in patients with ALI or ARDS
· Insure discontinuation of mechanical ventilation and/or extubation occur at the earliest possible time

Protocol Rationale

There exists Level 1 research evidence supporting a lung protective strategy using low-tidal volume (Vt) ventilation in patients meeting criteria for ALI or ARDS. Described in detail at http://hedwig.mgh.harvard.edu/ardsnet/studies.html, this strategy demonstrated a 23% reduction in mortality in patients treated with a protocol designed to limit alveolar stretch using a tidal volume of 6 mL/kg compared to subjects ventilated at a tidal volume of 12 mL/kg.1

It remains unknown if there exists any benefit to higher levels of PEEP compared with higher levels of FiO2 in patients with ALI or ARDS. The only available Level 1 evidence comparing higher levels of PEEP to higher inspired oxygen concentrations with lower levels of PEEP suggests there is no benefit to one strategy or the another. This randomized controlled trial was stopped due to lack of efficacy after enrollment of 550 patients and has not yet been published (http://hedwig.mgh.harvard.edu/ardsnet/ards04.html).

In patients without ALI or ARDS, no specific mode of mechanical ventilation is known to offer any advantage. As such, the decision about the mechanical ventilation mode is left to physician discretion. Once a patient is ready to wean, it appears that a daily trial of spontaneous ventilation offers the greatest potential for early extubation. This approach is superior to gradual withdrawal of ventilation using pressure support or intermittent mandatory ventilation.2-5 In patients requiring prolonged ventilation, there is no conclusive evidence that airway management (intubation versus "early" tracheostomy) has an impact on outcome.

Protocol Summary

· Patients with ALI or ARDS as defined by a PaO2/FiO2 £300 and bilateral pulmonary infiltrates are managed by following a low tidal volume, lung protective mechanical ventilation strategy with the expectation this lung protective strategy is achieved (i.e. Vt <6 mL/kg) within 24 hours of meeting ALI criteria.

· Patients without ALI are managed by conventional mechanical ventilation. The specific mode of mechanical ventilation is left to physician discretion. Should ALI criteria be met subsequently, the patient is managed utilizing the low tidal volume strategy.

· Once the patient meets readiness to wean criteria, a daily trial of spontaneous breathing is performed. If this trial is successful, it is expected that the patient is extubated or otherwise liberated from mechanical ventilation.

· If readiness to wean criteria are met, but the patient is not likely to be successfully liberated from mechanical ventilation or does not demonstrate the

ability to protect the airway, a procedure for gradual reduction in ventilatory support is instituted consistent with patient tolerance. The specific mode of weaning is left to physician discretion.

· All patients who meet readiness to wean criteria, but are not successfully liberated from mechanical ventilation after the weaning process receive sufficient mechanical ventilatory support overnight to rest and prevent occult fatigue.

· The cycle of spontaneous trials of breathing, weaning and rest are continued daily until the patient is liberated from mechanical ventilation.

· Airway management strategies (continued endotracheal intubation versus tracheostomy) are left to treating physician discretion.

Protocol Details

Patients with Acute Lung Injury or Acute Respiratory Distress Syndrome

Initial Ventilator Settings

· Tidal volume (Vt)
Vt calculations are based on predicted body weight (PBW) as follows:
o For males: PBW (kg) = 50 + 2.3 [height (inches) – 60]
o For females: PBW (kg) = 45.5 + 2.3 [height (inches) – 60]
Initial Vt is set at 8 mL/kg PBW. This setting is reduced by 1 mL/kg PBW at intervals of <2 hours until Vt = 6 mL/kg PBW.

· Ventilator rate
Initial ventilator rate is set at 12-20 breaths per minute if possible. Maximum rate setting is 35 breaths/minute.

Subsequent Ventilator Adjustments

Ventilator rate and tidal volume are adjusted to achieve arterial pH and end-inspiratory plateau pressure goals, respectively.

· Arterial pH
The goal is to maintain the arterial pH between 7.25 and 7.45. Arterial pH is measured upon admission to the ICU and then every morning as well as 15 minutes after every change in tidal volume or respiratory rate. The clinical setting and physician discretion dictate additional measurements. Suggested management of alkalemia and acidemia is as follows:

o Alkalemia (pH >7.45) ® Decrease ventilator rate.
o Mild acidemia (7.15 ³ less than or equal to pH <7.25) ® Increase ventilator rate

up to maximum of 35 or until pH >7.25 or PaCO2 <25 mm Hg. If ventilator rate = 35 or PaCO2 <25, then bicarbonate infusion may be administered.
o Severe acidemia (pH <7.15) ® Increase ventilator rate to 35. If ventilator rate = 35 and pH <7.15 and bicarbonate has been considered or infused, then tidal volume may be increased by 1 ml/kg until pH >7.15. Under these conditions, the target plateau pressure described below may be exceeded.

· End-inspiratory plateau pressure goals: £30 cm H2O

o Plateau pressures are measured and recorded every eight hours and 1-5 minutes after each change in PEEP or tidal volume. For each measurement, patients must be relaxed, not coughing or moving. The pressure corresponding to the first plateau that occurs after initiating a 0.5 second pause is recorded. The pause is removed for at least 6 breaths, and repeated at least twice. The mean of at least 3 replicates represents the plateau pressure.

o If plateau pressures cannot be measured because of air leaks, then peak inspiratory pressures are substituted.

o Tidal volumes are reduced by 1 mL/kg PBW q2 hours if necessary to maintain plateau pressures less than or equal to 30 cm H2O (If arterial pH <7.15, tidal volume needs not be reduced; see "suggested management of severe acidemia"). Measure arterial pH 15 minutes following every change in tidal volume.

o The minimum tidal volume is 4 mL/kg PBW. If the tidal volume is less than 6 mL/kg and plateau pressure is < 25 cm H2O then Vt is increased in 1mL/kg PBW increments until plateau pressure is 25 - 30 cm H2O or Vt = 6 mL/kg PBW.

· Oxygenation
Target ranges for oxygenation are 55 mm Hg is less than or equal to PaO2 is less than or equal to 80 mm Hg, or 88% is less than or equal to SpO2 is less than or equal to 95%. When PaO2 and SpO2 measurements are available simultaneously, the PaO2 measurement takes precedence. When oxygenation goals are achieved, the FiO2 should be weaned down to <0.6 at the earliest possible time. The PEEP and FiO2 combinations used to achieve the goals above are left to physician discretion, but as a general rule the FiO2 (as a percentage) to PEEP ratio should be less or equal to 5.

When increasing PEEP above 10 cm H2O, do so by 2-5 cm H2O increments to a maximum of 35 cm H2O or until PaO2 = 55-80 mm Hg or SpO2 = 88-95%. If the PEEP increase does not lead to an increase in PaO2 of > 5 mm Hg within 4 hours, PEEP is set to the last level that achieved a response.

o Arterial oxygenation can be assessed by either SpO2 or PaO2 at a minimum of every 4 hours.

o If arterial oxygenation is not within the target range, then either FiO2 or PEEP

should be adjusted within 30 minutes. Following adjustment, oxygenation is reassessed within 15 minutes and subsequent adjustments are made if necessary.

o If PaO2 <55 mm Hg or SpO2 <88% and tidal volume = 4 mL/kg PBW (or the minimum tidal volume necessary for pH control) and plateau pressure >30 cm H2O, then FiO2 is raised until PaO2 = 55-80 mm Hg or SpO2 = 88-95% or FiO2 = 1.0. If PaO2 <55 mm Hg or SpO2 <88% and FiO2 = 1.0, PEEP is raised to achieve adequate oxygenation. In these circumstances, plateau pressure may exceed 30 cm H2O. Brief periods (5 – 10 minutes) of SpO2 <88% or >95% may be tolerated without making changes in PEEP or FiO2. FiO2 = 1.0 may be used for brief intervals (10 minutes) of transient desaturation or to prevent desaturation during treatments such as tracheo-bronchial suctioning or position changes.

o Changes in more than one ventilator setting driven by measurements of PO2, pH, and plateau pressure may be performed simultaneously if necessary.

Assessment of readiness to wean

Patient assessment of the following criteria should be performed each day between the hours of 0400 and 0800. If the assessment is precluded by procedures or other extenuating circumstances, the assessment and initiation of weaning procedures may occur later in the day, but should not be held off to the next day.

A. Resolution or stabilization of the underlying disease process leading or contributing to the requirement for mechanical ventilation
B. Not receiving neuromuscular blocking agents and without residual effects of neuromuscular blockade
C. Exhibiting respiratory efforts
D. Hemodynamically stable with no inotropic or vasopressor support (less than or equal to 5 µg/kg/min of dopamine or dobutamine will not exclude patients from consideration for liberation).
E. FiO2 less than or equal to 0.5 and PEEP less than or equal to 10 cm H2O
F. PaO2 >75 mmHg
G. Ve <15 L/min
H. Ve >80% of Ve mechanical
I. pH between 7.30 and 7.50

If criteria A through I are met, assess the ability to tolerate a trial of spontaneous breathing. If the patient is not ready to wean by the criteria described above, then return to the previous mode of ventilator support and reassess readiness to wean daily.

Trial of spontaneous breathing protocol

All patients receiving mechanical ventilation who are considered ready to wean are evaluated on a daily basis for the ability to tolerate unassisted ventilation by means of a 30-90 minute trial of spontaneous breathing between the hours of 0500 and 0900. If circumstances preclude the conduct of the trial at this time of day, the assessment and trial can be performed later in the day, but should not necessarily be held off to the next day. A trial is attempted unless there is a physician order to delay the trial.

· A 30-90 minute trial of spontaneous breathing is performed with the continuous positive airway pressure (CPAP) setting set to the current PEEP setting, no greater than an inspiratory pressure support of 8 cm H20 and FiO2 equal to current FiO2. (FiO2 at the initiation of the trial may be increased by 0.1 above previous FiO2 at the discretion of the physician.)

· If the patient meets any one of the criterion below, the trial is terminated and the patient is returned to the previous ventilator settings:
o Respiratory rate >35 for ³5 minutes
o SpO2 <90% for ³30 seconds
o Heart rate >140 beats/minute or sustained heart rate increase or decrease of 20% from baseline; systolic BP >180 mm Hg or < 90 mm Hg
o Sustained increase in anxiety, diaphoresis, or other signs of respiratory distress
o Cardiac instability or dysrhythmias
o pH less than or equal to 7.32

· The patient should be evaluated for transient issues that may negatively influence a trial of spontaneous breathing (that is, excess sedation, agitation, acidemia, etc.). In these cases, another assessment should be made later in the day when the issue has been resolved. Otherwise, the patient should be returned to the previous mechanical ventilator settings and weaning commenced as ordered by the attending physician.

Assessment of readiness for extubation

If the patient successfully completes a trial of spontaneous breathing, the following criteria should be assessed to determine readiness for extubation:
· Does not require suctioning more than every 4 hours
· Anticipated good spontaneous cough
· Endotracheal tube cuff leak with less than or equal to 30 cm H2O positive pressure
· No known history of upper airway obstruction or stridor within the prior 48 hours
· No known history of reintubation for bronchial hygiene within the prior 48 hours

The therapist should notify the primary physician team of the protocol success and discuss readiness for extubation criteria. If the physician decides not to extubate, the patient may be placed on a T-piece, with CPAP equal to the PEEP

setting on the ventilator or on a low level of pressure support (PS <8).

For the purposes of this protocol, all of the following are considered unassisted breathing:
· Extubated with face mask, nasal prong oxygen, or room air, OR
· T-tube breathing, OR
· Tracheostomy mask breathing, OR
· CPAP=5 without PS (PS >8) or intermittent mandatory ventilation (IMV) assistance

If the patient fails the trial of spontaneous breathing, the patient may be weaned using a mode of ventilation prescribed by the treating physician. The patient must rest overnight and another assessment of readiness to wean and a trial of spontaneous breathing (if ready to wean) should be conducted the following morning.

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Accompanying Documents

TR2.1 Mechanical Ventilation Protocol Pocket Card 3x5 Inch Side 1
TR2.1 Mechanical Ventilation Protocol Pocket Card 3x5 Inch Side 2

Published on www.gluegrant.org in May 2004 by the Inflammation and the Host Response to Injury Investigators.
Supported by a Large-Scale Collaborative Project Award (U54-GM62119) from The National Institute of General Medical Sciences.

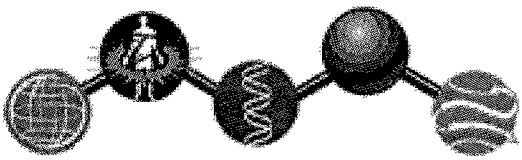
TR2.1 Mechanical Ventilation Protocol 3x5 Inch Pocket Card
Inflammation and the Host Response to Injury

Patients with ALI or established ARDS ($PaO_2/FiO_2 \leq 300$, bilateral pulmonary infiltrates) aim for the following within 24 hrs of meeting criteria:

- Initial tidal volumes may be set at 8 mL/kg predicted body weight (PBW); tidal volumes should be reduced by 1 mL/kg at intervals of <2 hours until the tidal volume =6 mL/kg. Tidal volume calculations are based on predicted body weight as follows:
  For males: PBW (kg) = 50 + 2.3 [height (inches) – 60]
  For females: PBW (kg) = 45.5 + 2.3 [height (inches) – 60]
- PaO_2 55-80 mm Hg or SpO_2 88%- 95%. FiO_2/PEEP ratio should be $\leq$5 and PEEP must be $\leq$35 cm H_2O
- pH 7.25-7.45 with RR <35 and $PaCO_2 \geq 25$. HCO_3 infusion may be given if necessary. If pH < 7.15 then Vt may be increased by 1 mL/kg to pH $\geq$7.15 and target plateau pressures (see below) may be exceeded
- Plateau pressures (PP) $\leq$30 cm H_2O. Reduce Vt to no less than 4 mL/kg. If Vt <6 mL/kg and PP <25 then increase Vt until PP= 25-30 or Vt = 6 mL/kg

Patients not meeting ALI/ARDS criteria can be ventilated using the mode, rate and tidal volume chosen at the treating physician's discretion.

Pocket Card formatted with Avery 5388 Laser Index Cards 3 cards/ sheet 3x5 in.



INFLAMMATION
& the Host Response to Injury

TR3: Clinical Protocol for the Prevention, Diagnosis and Treatment of Ventilator-Associated Pneumonia

The contents of this protocol were developed by the Inflammation and the Host Response to Injury Large-Scale Collaborative Research Program under a grant from the National Institute of General Medical Sciences. If any material from this protocol is used, proper credit to the Program and the NIGMS must be given.

Summary

This protocol addresses ventilator-associated pneumonia (VAP). Prevention of VAP is best accomplished through adequate hand washing, inclining the patient 30 degrees or more, avoiding gastric overdistention, and maintaining the patient's oral hygiene. Various clinical criteria can be used to diagnose VAP. Patients with a threshold clinical pulmonary infection score (CPIS) greater than 6 should be evaluated for pneumonia. Quantitative protected sampling of the lower respiratory tract can help distinguish between colonization and infection. In contrast, quantitative endotracheal aspiration cannot be considered sensitive or specific enough to accurately diagnose VAP. Quantitative protected-specimen brush obtained via bronchoscopy may be useful, but both the sensitivity and specificity of this analysis varies considerably among patients. It is critical that treatment of suspected VAP should begin with early, empiric therapy targeted to common organisms, as defined by the local antibiogram for the unit in question. Inadequate antibiotic coverage significantly increases mortality in these patients. On the other hand, if no sign of infection is found, antibiotic therapy should be halted so as to prevent superinfection and secondary pneumonia from resistant organisms.

Protocol Goals

· Describe techniques utilized to minimize the incidence of VAP
· Define the minimal criteria to meet the diagnosis of VAP
· Describe the general regimens used in the treatment of VAP

Protocol Rationale

This protocol is based on available published literature recognizing the criteria that define VAP are not clearly standardized. It should be recognized that even when there are "good" data to support guidelines for the management of VAP, the patient populations studied in the literature were seldom severely injured patients for the most part.

Prevention of VAP

The following recommendations, published by the Centers for Disease Control and Prevention (CDC) and available at http://www.cdc.gov/, are supported by at least one randomized, controlled trial.

· Adequate hand washing between patients.
· Semi-recumbent positioning of the patient to >30 degrees.
· Avoidance of gastric over-distention.
· Routine oral hygiene as a part of daily care

Diagnosis of VAP

There are no "gold standard" criteria that define VAP. Initial calculation of a CPIS is used to screen patients for presumed VAP.1 Use of this score allows comparison of patients treated for pneumonia across study sites. Patients with a CPIS of <6 have little chance of having pneumonia in a group of hospitalized medical patients. Patients with a CPIS >6 are evaluated for pneumonia. The rationale is that there is no microbiological diagnostic test that is 100% specific for VAP and use of this score threshold minimizes the risk that patients with few clinical signs and symptoms of VAP will have false-positive culture results with subsequent administration of antibiotics.2

Recent studies to evaluate criteria for treatment with antibiotics for a presumed

diagnosis of VAP have utilized data from quantitative protected sampling of the lower respiratory tract. Quantitative cultures, while not 100% sensitive and specific, can help distinguish between colonization and infection. Identification of the most likely organism can lead to antibiotic de-escalation once sensitivities are known. These studies suggest that clinical management strategies based on an invasive diagnostic procedure (bronchoalveolar lavage [BAL] or protected specimen brush [PSB]) leads to improved survival and decreased antibiotic complications compared with a strategy based on clinical guidelines without protected lower respiratory tract sampling.3

There are a number of techniques that can be utilized for quantitative evaluation. Quantitative endotracheal aspiration cannot be considered sensitive or specific enough to accurately diagnose VAP. The sensitivity of quantitative BAL obtained via bronchoscopy ranges from 42 to 93% (mean, 73%) and the specificity ranges from 45 to 100% (mean, 82%). The sensitivity of quantitative PSB obtained via bronchoscopy ranges from 33 to 100% (mean, 67%) and the specificity ranges from 50 to 100% (mean, 95%). Finally, blinded specimen collection techniques demonstrate sensitivity that ranges from 60 to 100% and specificity that ranges from 70 to 100%.

The threshold values used for a positive quantitative culture are those values presently used by the CDC and generally accepted in the medical literature (available at http://www.cdc.gov/ ncidod/hip/nnis/members/members.html).

Treatment of VAP

Treatment of suspected VAP should begin early with empiric therapy directed at the typical antiobiogram for the given unit location. At least 4 studies have shown if the initial antibiotic therapy is inadequate to cover the organisms that are ultimately isolated, then mortality is significantly increased.4 Further, if antibiotic selection is either withheld or escalated once the culture results are known, mortality is still greater than if the correct antibiotic selection had been made empirically at the start of treatment.

Discontinuation of antibiotics if BAL cultures are negative is supported in the literature. It has also been shown that unnecessary use of antibiotics for VAP increases the likelihood of superinfection with multi-resistant organisms. Recent data suggest that antibiotics can be stopped once clinical signs of infection have resolved rather than fixed duration of antibiotic therapy. Discontinuation of antibiotics may also decrease the incidence of secondary pneumonias with multi-resistant organisms.5

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Unnumbered Reference

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Accompanying Document

TR3.1 Ventilator-Assisted Pneumonia Flowchart

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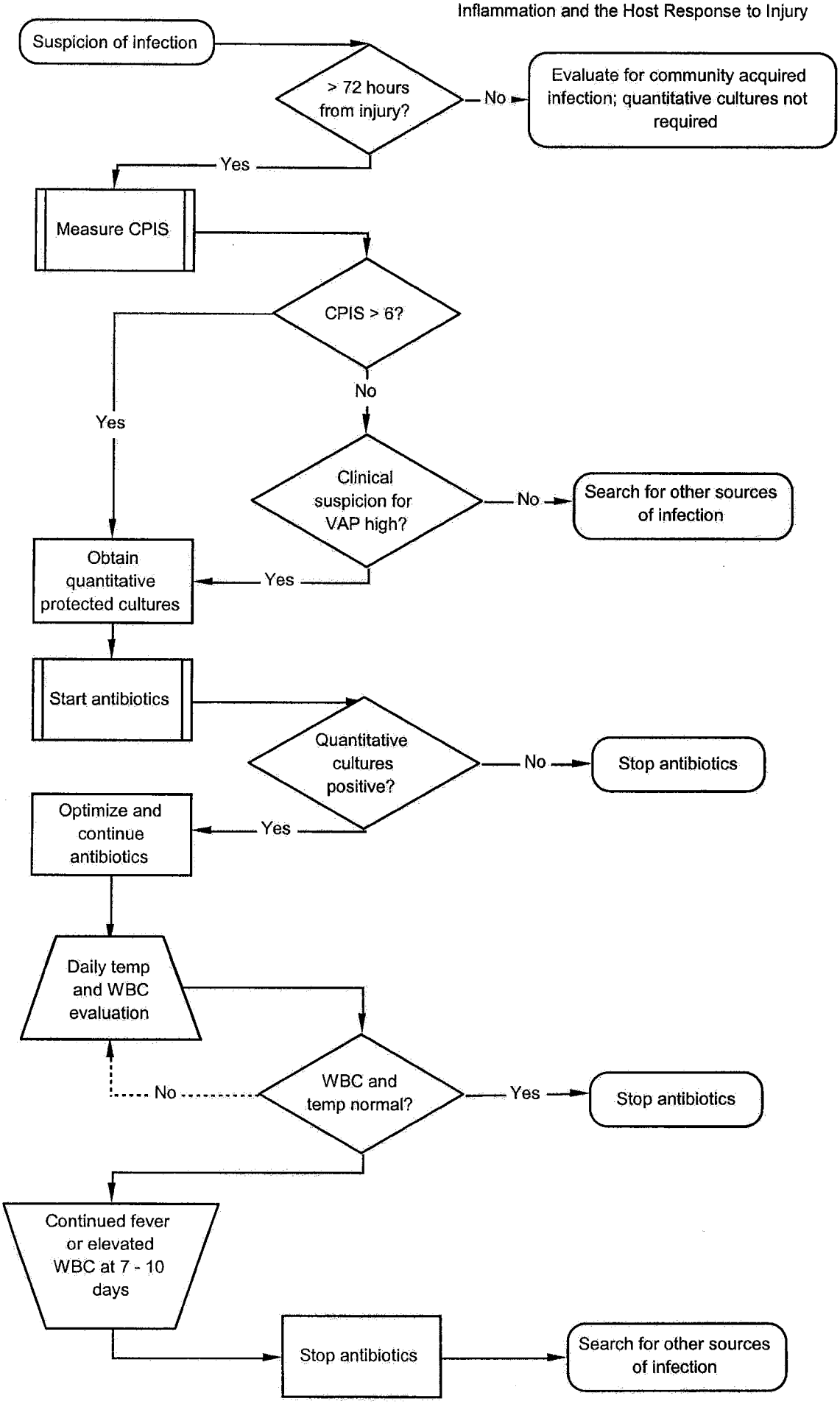
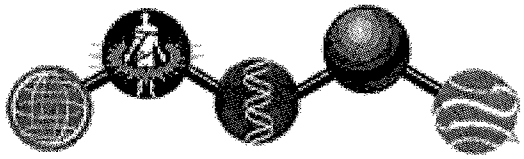
Supported by a Large-Scale Collaborative Project Award (U54-GM62119) from The National Institute of General Medical Sciences.

TR3.1 Ventilator-Associated Pneumonia Flowchart
Inflammation and the Host Response to Injury





INFLAMMATION
& the Host Response to Injury

TR4 ICU Insulin Infusion Orders

GOAL: BLOOD GLUCOSE 80-110MG/dL

1. Indications: Critically ill patients with persistent blood glucose >110mg/dL

2. Monitoring:

- check blood glucose q 2 hrs and q 1 hr prn
- If tube feeds, TPN or fluids with D5W are stopped; decrease insulin infusion rate by 50% and check blood glucose q 1 hr
- **If blood glucose decreases by >50mg/dL and is still elevated** keep infusion at current rate and recheck blood glucose in 1 hour
- Do NOT bolus for Serum Creatinine (SCr) >2

3. Initiation:

Blood Glucose (mg/dL)	Bolus IV Push (units)	Infusion Rate (units/ hour)
111-150	2	1
151-200	2	2
201-250	4	2
251-300	6	4
301-350	8	4
>350	10	4

4. Continuation of insulin infusion:

Blood Glucose(mg/dL)	Bolus IV Push (units)	Infusion Rate(units/hour)
< 60	0	D/c infusion; give ½ ampule D50 IV push; recheck blood glucose in 30 minutes AND if blood glucose >80, resume insulin infusion at 50% of previous rate
60-79	0	D/c infusion; recheck blood glucose in 30 minutes AND if blood glucose > 80, resume insulin infusion at 50% of previous rate
80-110	0	No change; if blood glucose continues to decrease within desired range over 4 hours; decrease rate by 20%**
111-150	0	increase rate by 20%**
151-200	2	increase rate by 20%**
201-250	4	increase rate by 20%**
251-300	6	increase rate by 20%**
301-350	8	increase rate by 20%**
>350	10	increase rate by 20%**

** See reverse for rounded rate adjustments of 20% (increase or decrease)

5. If infusion rate = 30units/hour; notify H.O. and continue to bolus per protocol as indicated by blood glucose. Do not increase infusion rate. Check blood glucose q 1 hr

**20% adjustments (in •/hr)

Current Rate	Increase Rate	Decrease Rate
0.5	1	0
1	1.5	0.5
1.5	2	1
2	2.5	1.5

2.5	3	2
3	3.5	2.5
3.5	4	3
4	5	3
4.5	5.5	3.5
5	6	4
5.5	6.5	4.5
6	7	5
6.5	8	5
7	8.5	5.5
7.5	9	6
8	9.5	6.5
8.5	10	7
9	11	7
9.5	11.5	7.5
10	12	8
10.5	12.5	8.5
11	13	9
11.5	14	9
12	14.5	9.5
12.5	15	10
13	15.5	10.5
13.5	16	11
14	17	11
14.5	17.5	11.5
15	18	12
15.5	18.5	12.5
16	19	13
16.5	20	13
17	20.5	13.5
17.5	21	14
18	21.5	14.5
18.5	22	15
19	23	15
19.5	23.5	15.5
20	24	16
20.5	24.5	16.5

21	25	17
21.5	26	17
22	26.5	17.5
22.5	27	18
23	27.5	18.5
23.5	28	19
24	29	19
24.5	29.5	19.5
25	30	20
25.5	30	20.5
26	30	21
26.5	30	21
27	30	21.5
27.5	30	22
28	30	22.5
28.5	30	23
29	30	23
29.5	30	23.5
30	30	24

Published on www.gluegrant.org by the Inflammation and the Host Response to Injury Investigators.
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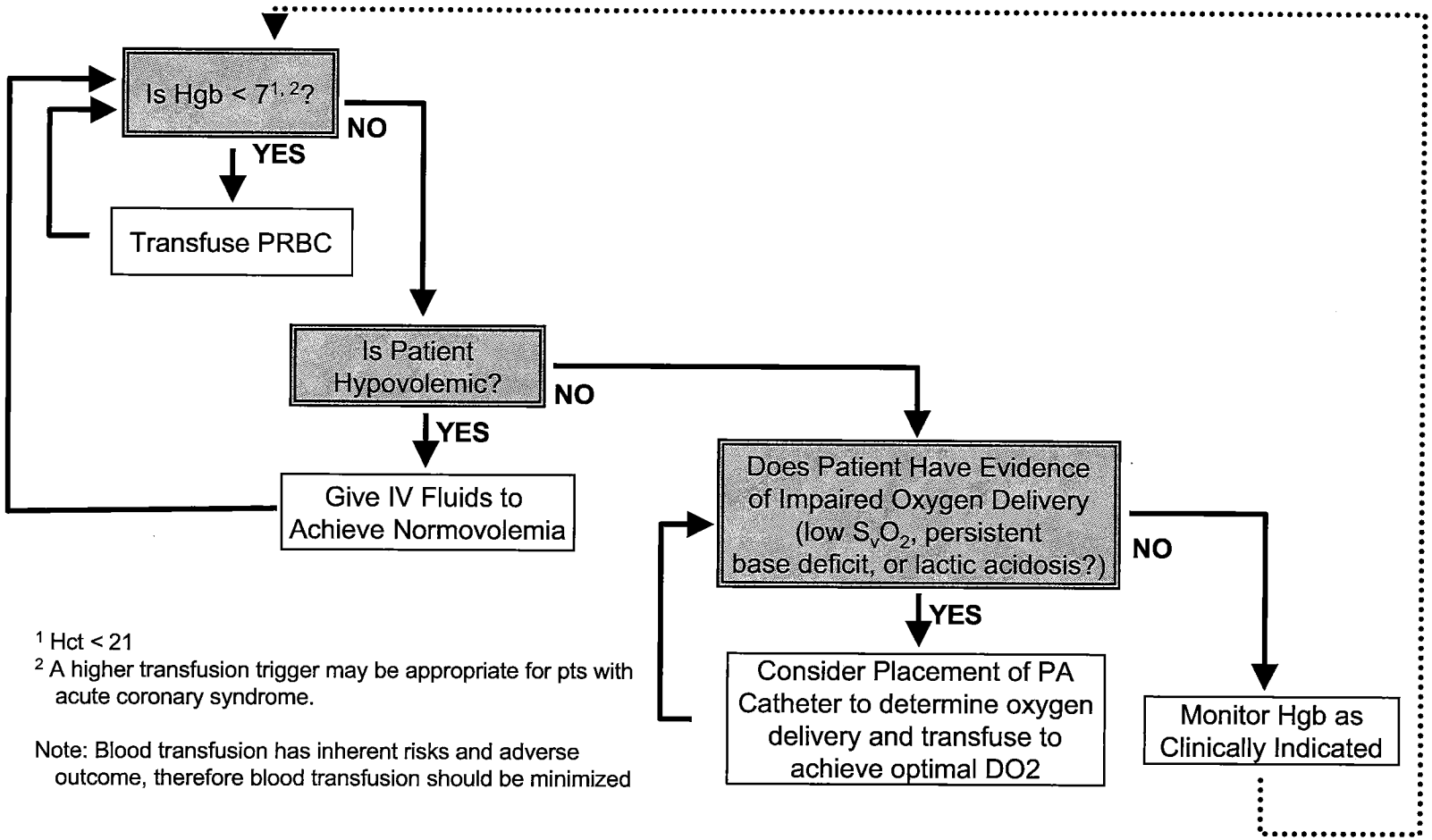
TR5 Transfusion Guidelines for Trauma Patient

(excludes immediate resuscitation)



[1] Hct < 21

[2] A higher transfusion trigger may be appropriate for pts with acute coronary syndrome.

Note: Blood transfusion has inherent risks and adverse outcome, therefore blood transfusion should be minimized

Rev 07/12/04

TR6 VTE Prophylaxis Algorithm
(Revision 07/12/04)

Traumatized patient with anticipated hospital length of stay exceeding 48 hours with one or more of the following:

(1) Pelvic or lower extremity fracture requiring operative fixation or bed rest > 2 days
(2) Spinal cord injury with complete or incomplete deficit
(3) Complex lower extremity venous injury
(4) Anticipated immobilization for > 2 days
(5) GCS < 9
(6) History of VTE, hypercoagulable state, or cancer
(7) Obesity (BMI ≥30)
(8) Age > 50
(9) ISS > 16
(10) Pregnancy

No → **Low risk of VTE** Consider mechanical prophylaxis[2] with/without heparin

Yes ↓

Potential contraindications to LMWH[1]:

(1) Severe head injury, intracranial hemorrhage, or craniotomy
(2) Epidural catheter or hematoma
(3) Ongoing hemorrhage or significant coagulopathy
(4) Intra-abdominal solid organ injury managed non-operatively
(5) Spinal column fracture

Yes → **Potential indication for Vena cava filter:**

(1) Spinal cord injury with paraplegia or quadriplegia
(2) Complex pelvic fractures with associated long-bone fractures
(3) Multiple long bone fractures
(4) Contraindication to LMWH expected to exceed 72 hours

Yes → Consider VCF[4] placement

No ↓

No ↓

LMWH[1] with mechanical prophylaxis[2]

Yes ↑

Contraindications to LMWH[1] resolve

No → Mechanical prophylaxis[2] with UFH[3]

No ↑

Suspicion of VTE

No ↑

Yes ↓

Diagnostic W/U

Negative ↑

Positive ↓

Contraindication to anticoagulation

No ↓ Therapeutic anticoagulation

Yes ↓ VCF[4] placement

Mechanical prophylaxis[2] with UFH[3] ↓

Doppler surveillance[5]

Negative ↑

Positive ↓

Notes:

[1]LMWH = Low Molecular Weight Heparin.
[2]Mechanical prophylaxis = TED and sequential compression devices or A-V foot pumps.
[3]UFH = Unfractionated Heparin.
[4]VCF = vena caval filter – permanent or temporary.
[5]Doppler surveillance = lower extremity doppler within 72 hours of admission then every 5 to 7 days.

TR7 Sedation Protocol
Draft (07/12/04)

Sedation/Analgesia Protocol for Mechanical Ventilation

Purpose: To provide a strategy for physician and nursing staffs to manage issues of sedation and analgesia in mechanically ventilated patients. These guidelines should direct the care of routine patients. They should be modified on the basis of clinical indication.

Goals: **1)** Sedation level should be recorded using an objective scoring instrument (e.g. Ramsey, Riker, Richmond scales). **2)** Unless medically contraindicated, the optimal target level of sedation is that at which the patient is alert, not agitated, and able to maintain brief eye contact and/or follow simple instructions.

Indications: All ICU patients who are mechanically ventilated.

Monitor: Assess pain and sedation every 15 min. until patient reaches desired level of sedation. Thereafter assess every 4 hrs unless otherwise indicated.

Exceptions: Patients who are allergic to any of the following agents.

Sedation Vacation: Unless medically contraindicated, sedation should be interrupted daily until the patient is awake (establish eye contact and/or follow simple instructions), or until the patient becomes agitated or uncomfortable.

Analgesia for PAIN:

Fentanyl: Bolus 25-100 mcq IV q 5 min to achieve specified goal. If goal met, continue bolus doses q 30-60 min. If goal not met after 3 hours begin infusion at 50 mcg/hr. If goal not met in 1 hr, bolus with amount of current rate and increase infusion by 25mcg/hr.

Sedation for ANXIETY: (choose one)

Lorazepam: Bolus 1-2 mg IV q 15 min prn. If goal met, continue bolus doses q 2-4 hr prn. If goal not met within 3 hours begin scheduled doses at 4 mg IV q 6 hrs and continue bolus doses. If goal not met in 24 hours, begin infusion at 2 mg /hr and continue bolus doses prn. If goal not met after 1 hour increase infusion rate by 1mg/hr and continue boluses prn. Consider contribution of pain and delirium to agitation.

Propofol: (Consider use if expected duration of mechanical ventilation < 48 hrs, or for Neurosurgical patients) Bolus 0.5 mg/kg IV, then infuse 20 mcg/kg/min. If goal not met in 15 minutes rebolus with 0.5 mg/kg over 2 minutes and increase infusion by 10 mcg/kg/min q 15 min to maximum 100 mcg/kg/min. Consider contribution of pain and delirium to agitation.

Antipsychotic for DELIRIUM:

Haloperidol : 2-10 mg IV q1 hr prn. If goal not met in 6 hours begin scheduled doses at 5 mg IV q 6 hrs and continue bolus doses.

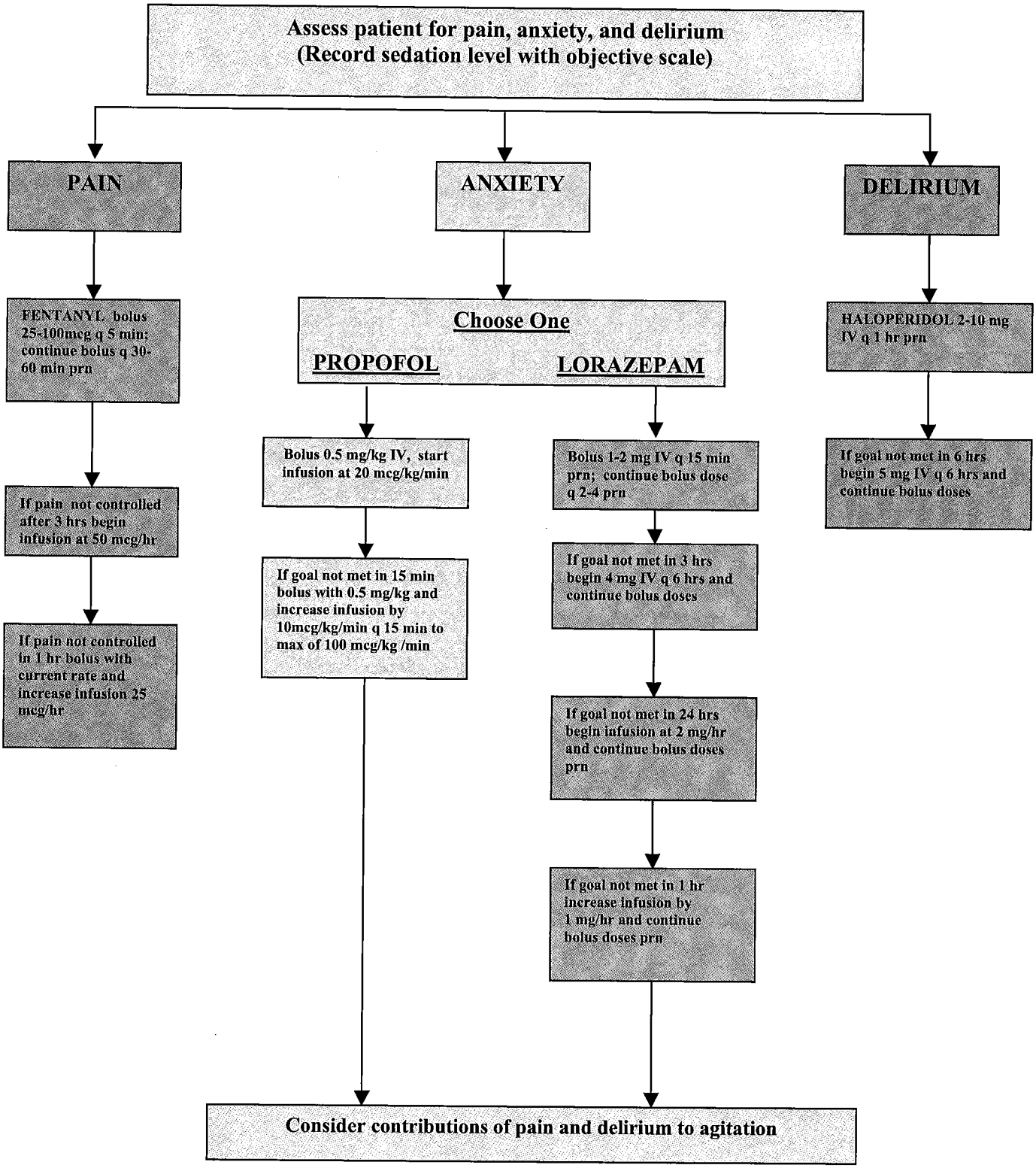
TR7 Sedation Protocol
Draft (07/12/04)

References:

1. Brook, Alan D et al. Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. Crit Care Med 1999 Vol. 27: 2609-2615.
2. Jacobi, Judith, et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med 2002 Vol. 30, No. 1: 119-141.
3. Kress, John P, et al. Daily Interupption of Sedative Infusions in Critically Ill Patients Undergoing Mechanical Ventilation. NEJM 2000 Vol.342: 1471-1477.

TR7 Sedation Protocol
Draft (07/12/04)

Sedation/Analgesia Protocol for Mechanical Ventilation



Guidelines for Management of Traumatic Brain Injury: Resuscitation Outcomes Consortium

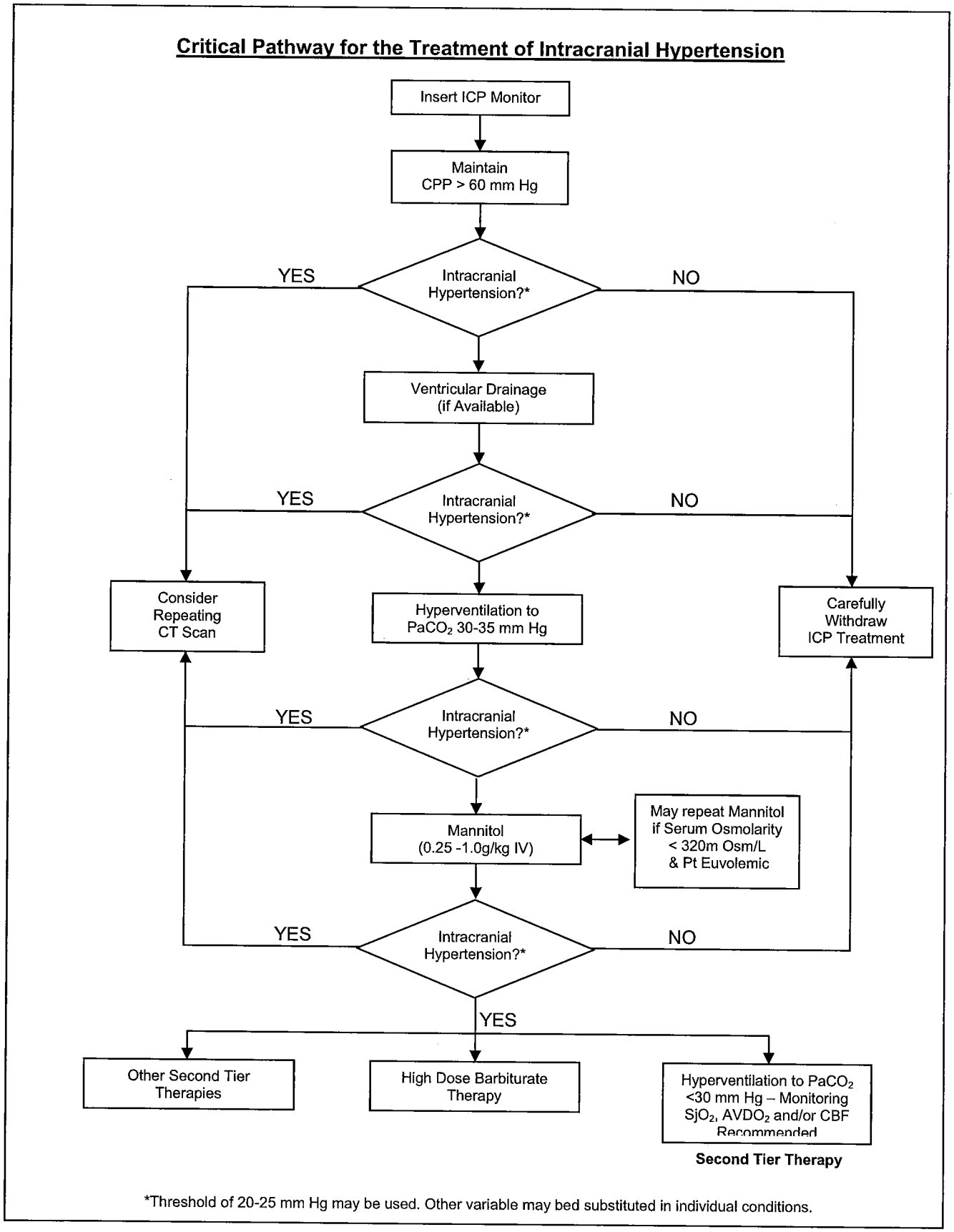
Monitoring & Management of Intracranial Pressure

All patients meeting the criteria for severe traumatic brain injury (persistent GCS <9) should have an intracranial pressure monitor placed.

Patients with a sustained ICP> 25 mmHg should have intervention aimed at lowering ICP. This intervention is at the discretion of the treating physician but guided by the Brain Trauma Foundation Guidelines (see below). Excess hyperventilation should be avoided unless the patient is showing signs of acute herniation. Patients should be resuscitated to avoid episodes of hypotension (SBP<90 mmHg).

Brain Trauma Foundation Guidelines

The Brain Trauma Foundation, by consensus, has developed a critical pathway for the treatment of established intra-cranial hypertension, which is printed on the following page. It should be viewed as a framework that may be useful in guiding an approach to treating intra-cranial hypertension. It can and should be modified in an individual case by any circumstances unique to the patient as well as by the response of the ICP to individual treatment steps.



Critical Pathway for the Treatment of Established Intracranial Hypertension in the severe head injury patient. Adapted from the Brain Trauma Foundation, Inc.

Appendix G

Pre-hospital script

Script for Prehospital Provider for Conscious, Alert, LAR at scene of injury

1. Your family member appears to have severe bleeding or a brain injury, may be in shock, and needs treatment with IV fluids.

2. As part of a research study, we are testing an investigational fluid called hypertonic saline believed to improve the chance of surviving and lessen brain injury.

3. The University of _____ is overseeing the research.

4. The risks of Hypertonic Saline are very rare and the study doctors believe that the benefits outweigh the risk.

5. Unless you object, your family member will be included in the study and get a hypertonic solution or regular IV fluids. All other medical care will be the same. Because treatment needs to start right away your must tell us now if you do not want him/her to be in the study.

Appendix H

Sample Consents

University of

Continued Participation Consent Form

Hypertonic Resuscitation following Traumatic Brain Injury

Investigators

24 hour Emergency Telephone Number:
Ask for the Pre-Hospital Research Coordinator on call

Researcher's Statement

We are asking you or your family member to be in a research study. The purpose of this consent form is to give you the information you will need to help you decide whether to be in the study or not. Please read the form carefully. You may ask questions about the purpose of the research, what we would ask you to do, the possible risks and benefits, your rights as a volunteer, and anything else about the research or this form that is not clear. When we have answered all your questions, you can decide if you want to be in the study or not. This process is called "informed consent". We will give you a copy of this for your records.

Purpose

Injury and lost blood from trauma can cause your body to be in shock (low blood pressure related to blood loss). This decreased blood flow can lead to organ damage. In order to restore the blood pressure and blood flow, the medics give fluids into the patients' veins as soon as possible. This is called "resuscitation". The fluid most commonly used is "isotonic" or one that is the same concentration as the blood. We are trying to determine if infusing a "hypertonic" fluid or one more concentrated than the blood can increase the blood pressure and restore blood flow more efficiently. The hypertonic fluids we are using are called hypertonic saline with dextran (HSD) and hypertonic saline (no dextran). Hypertonic saline is a salt solution that is slightly more concentrated than your blood. Dextran is a sugar solution.

The medics noted in the field that you were in shock. Because the fluid resuscitation needed to start immediately we were unable to talk to you about enrollment into this study. An Institutional Review Board (IRB) has given us permission to do this study, in which subjects are enrolled without their consent due to the emergency nature of their illness. The review board here is the Human Subject's Division at the University of They oversee the safety of subjects in medical research.

This study will enroll 2122 patients in 10 medical centers across the United States and Canada. This study will enroll 300 patients here in . One third will receive the traditional resuscitation with isotonic fluid and one third will receive the experimental hypertonic fluid with dextran (HSD), and one third will receive the experimental hypertonic fluid without dextran (HS).

Benefits

You or your family member may not directly benefit from this study.
There are several potential benefits for society:

- If the use of HSD or HS improves tissue and organ perfusion (blood flow and delivery of oxygen) following shock and allows your body to more effectively fight infection.
- If HSD or HS improves outcome following brain injury by preventing swelling in the brain commonly seen following fluid resuscitation.

Procedures

If you agree to continue in this study your medical and surgical care will not be changed. You were enrolled in the study by the medics following your injury. You received either 250 cc (about one cup) of HSD or HS followed by standard fluid resuscitation or 250 cc of an isotonic solution (normal saline) followed by standard fluid resuscitation. This is by chance, like flipping a quarter. You, your physicians and the investigators for this study do not know which resuscitation fluid you received.

This study lasts for 28 days. We will continue to collect information from your medical record including laboratory values, reports of infection, blood pressure, heart rate, respiratory rate and temperature. We will collect this information to see how you are doing while you are in this study. If you leave Medical Center before day 28 we would like permission to phone you at home or to see you during a clinic visit. We will ask if you have experienced any problems since leaving the hospital. With your permission we will also contact you with a phone call interview at 6 months following your injury. This will take approximately 30 minutes and will ask how you are doing. We will ask how you perform regular daily activities. For example we will ask you about eating, drinking and personal hygiene activities, like washing your face and brushing you teeth. You have the right to refuse to answer any of the questions.

Risks, Stress, or Discomfort

During this study you may or may not have received HSD or HS. Participation in this study may involve some added risks or discomforts, although HSD has been tested in over 500 subjects in 8 clinical trials with no adverse effects reported.
Adverse events might include:

1. High sodium blood levels (Na> 160mEq/L) that could contribute to seizures requiring medical treatment.
2. Unexplained difficulties with blood clotting capabilities.
3. Skin irritation at the site of infusion or a rash due to a minor allergic reaction with no effects on you blood pressure or heart rate.
4. As is possible with any drug, you may have an allergic reaction (including severe immediate reactions) that we do not know about.
5. Whenever personal information is collected, there is always the potential that someone who is not authorized by this consent form may see your information. However, steps will be taken to minimize this risk.

If you have had any injury, bad effect, or any other unusual health experience you think may be from the study, make sure you tell the nurses or the study investigator

Other Information

Regardless of whether or not you choose to continue in this study, you will receive the same level of care. Declining to continue in the study has no effect on how you will be treated by the doctors currently providing care. You have the right to change your mind about participating in this study. If you do change your mind, contact

In the event of physical injury as a direct result of being in this study, medical care will be provided by a member of the investigating team or your clinical care team at no cost to you within the limits of the University of Compensation Plan.

There is no cost to you for participating in this study. When you complete your 6-month interview you will receive $50.00 in compensation for your time.

We have obtained a Certificate of Confidentiality from the Federal Government. A Certificate of Confidentiality protects your privacy by allowing us to refuse to disclose your name or other identifying information to anyone outside this research project. In the unlikely event of an audit by our funding agency (the National Institutes of Health), we may have to reveal your name, but only to the agency's authorized personnel.

If we disclose information about you to someone else it may no longer be protected the privacy law.

We do make every effort to keep the information about you confidential. You have been assigned a code number. This code number is used on all of the data we collected. A key linking you to the code number is kept locked in a secure location and will be available only to the investigators. Once this study is completed (2009) this key will be destroyed. If you have been discharged from Medical Center before day 28, we will contact you to see how you are doing. We will ask if you have seen any physicians or been back to the hospital since leaving. We will either see you at a follow-up clinic visit or contact you by phone for this information. In addition we will contact you in 6 months and to assess your neurologic function.

Data from this study, without your identity, may be reported in scientific meetings, articles or other appropriate communications.

For additional information about this study, please visit our website at:

A copy of this consent will be placed in your medical record.

If, during the course of the study, new information becomes available, we will provide it to you.

Date_____ Investigator's Name_____

Investigator's Signature_____

Subject's Statement

The study described above has been explained to me. I voluntarily consent to:

€Yes €No I agree to participate in a follow up phone call 28 days after my accident

€Yes €No I agree to participate in a phone call interview 6 months from now to assess my recovery

I have had an opportunity to ask questions. If I have any other questions in the future about the research I can contact one of the Investigators listed on the first page. If I have any questions about my rights as a research subject, I can call the Human Subjects Division at the University of . I will receive a copy of this consent.

Date_____ Subject's Name_____

Subject's Signature_____

Parental Signature (if subject is a minor) _____

For patients who are unable to sign due to the nature of their illness, I as the next of kin or legal guardian wish to voluntarily enroll him/her in this study. I have had the opportunity to ask questions. If I have questions about the research I may contact one of the Investigators listed on the first page. If I have any questions about my next of kin's rights as a research subject, I can call the Human Subjects Division at the University o.

I have received a copy of this consent.

Date_____ Legally Authorized Representative_____

Signature Legally Authorized Representative_____

For subjects and/or LAR who are unable to read and/or sign, I witness this consent.

Date_____ Witness Name_____

Witness Signature_____

CC: Subject Medical Record
Subject

University of

Continued Participation Consent Form

Hypertonic Resuscitation following Traumatic Injury

Investigators

24 hour Emergency Telephone Number:
Ask for the Pre-Hospital Research Coordinator on call

Researcher's Statement

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Purpose

Injury and lost blood from trauma can cause your body to be in shock (low blood pressure related to blood loss). This decreased blood flow can lead to organ damage. In order to restore the blood pressure and blood flow, the medics give fluids into the patients' veins as soon as possible. This is called "resuscitation". The fluid most commonly used is "isotonic" or one that is the same concentration as the blood. We are trying to determine if infusing a "hypertonic" fluid or one more concentrated than the blood can increase the blood pressure and restore blood flow more efficiently. The hypertonic fluids we are using are called hypertonic saline with dextran (HSD) and hypertonic saline (no dextran). Hypertonic saline is a salt solution that is slightly more concentrated than your blood. Dextran is a sugar solution.

The medics noted in the field that you were in shock. Because the fluid resuscitation needed to start immediately we were unable to talk to you about enrollment into this study. An Institutional Review Board (IRB) has given us permission to do this study, in which subjects are enrolled without their consent due to the emergency nature of their illness. The review board here is the Human Subject's Division at the University of . They oversee the safety of subjects in medical research.

This study will enroll 3726 patients in 10 medical centers across the United States and Canada. This study will enroll 500 patients here in . One third will receive the traditional resuscitation with isotonic fluid and one third will receive the experimental hypertonic fluid with dextran (HSD), and one third will receive the experimental hypertonic fluid without dextran (HS).

Benefits

You or your family member may not directly benefit from this study.
There are several potential benefits for society:

- If the use of HSD or HS improves tissue and organ perfusion (blood flow and delivery of oxygen) following shock and allows your body to more effectively fight infection.
- If HSD or HS improves outcome following brain injury by preventing swelling in the brain commonly seen following fluid resuscitation.

Procedures

If you agree to continue in this study your medical and surgical care will not be changed. You were enrolled in the study by the medics following your injury. You received either 250 cc (about one cup) of HSD or HS followed by standard fluid resuscitation or 250 cc of an isotonic solution (normal saline) followed by standard fluid resuscitation. This is by chance, like flipping a quarter. You, your physicians and the investigators for this study do not know which resuscitation fluid you received.

This study lasts for 28 days. We will continue to collect information from your medical record including laboratory values, reports of infection, blood pressure, heart rate, respiratory rate and temperature. We will collect this information to see how you are doing while you are in this study. If you leave Medical Center before day 28 we would like permission to phone you at home or to see you during a clinic visit. We will ask if you have experienced any problems since leaving the hospital.

Risks, Stress, or Discomfort

During this study you may or may not have received HSD or HS. Participation in this study may involve some added risks or discomforts, although HSD has been tested in over 500 subjects in 8 clinical trials with no adverse effects reported.
Adverse events might include:

1. High sodium blood levels (Na> 160mEq/L) that could contribute to seizures requiring medical treatment.
2. Unexplained difficulties with blood clotting capabilities.
3. Skin irritation at the site of infusion or a rash due to a minor allergic reaction with no effects on you blood pressure or heart rate.
4. As is possible with any drug, you may have an allergic reaction (including severe immediate reactions) that we do not know about.
5. Whenever personal information is collected, there is always the potential that someone who is not authorized by this consent form may see your information. However, steps will be taken to minimize this risk.

If you have had any injury, bad effect, or any other unusual health experience you think may be from the study, make sure you tell the nurses or the study investigator Dr.

Other Information

Regardless of whether or not you choose to continue in this study, you will receive the same level of care. Declining to continue in the study has no effect on how you will be treated by the doctors currently providing care. You have the right to change your mind about participating in this study. If you do change your mind contact

There is no cost to you for participating in this study.

In the event of physical injury as a direct result of being in this study, medical care will be provided by a member of the investigating team or your clinical care team at no cost to you within the limits of the University of Compensation Plan.

We have obtained a Certificate of Confidentiality from the Federal Government. A Certificate of Confidentiality protects your privacy by allowing us to refuse to disclose your name or other identifying information to anyone outside this research project. In the unlikely event of an audit by our funding agency (the National Institutes of Health), we may have to reveal your name, but only to the agency's authorized personnel.
If we disclose information about you to someone else it may no longer be protected the privacy law.

We do make every effort to keep the information about you confidential. You have been assigned a code number. This code number is used on all of the data we collected. A key linking you to the code number is kept locked in a secure location and will be available only to the investigators. Once this study is completed (2010) this key will be destroyed. If you have been discharged from Medical Center before day 28, we will contact you to see how you are doing. We will ask if you have seen any physicians or been back to the hospital since leaving. We will either see you at a follow-up clinic visit or contact you by phone for this information.

For additional information about this study, please visit our website at

A copy of this consent will be placed in your medical record.

Data from this study, without your identity, may be reported in scientific meetings, articles or other appropriate communications.

If, during the course of the study, new information becomes available, we will provide it to you.

Date_____ Investigator's Name_____

Investigator's Signature_____

Subject's Statement

The study described above has been explained to me. I voluntarily consent to participate in this activity. I have had an opportunity to ask questions. I give the investigators permission to review my medical records as described above. If I have any other questions in the future about the research I can contact one of the Investigators listed on the first page. If I have any questions about my rights as a research subject, I can call the Human Subjects Division at the University I will receive a copy of this consent.

€Yes €No I agree to the blood draws as described above

€Yes €No I agree to participate in a follow up phone call 28 days after my accident

Date_____ Subject's Name_____

Subject's Signature_____

Parental Signature (if subject is a minor)_____

For patients who are unable to sign due to the nature of their illness, I as the next of kin or legal guardian wish to voluntarily enroll him/her in this study. I have had the opportunity to ask questions. I give my permission for the investigators to review his/her medical records as described above. If I have questions about the research I may contact one of the Investigators listed on the first page. If I have any questions about my next of kin's rights as a research subject, I can call the Human Subjects Division at the University of '

I have received a copy of this consent.

Date_____ Legally Authorized Representative_____

Signature Legally Authorized Representative_____

For subjects and/or LAR who are unable to read and/or sign, I witness this consent.

Date_____ Witness Name_____

Witness Signature_____

CC: Subject Medical Record
Subject

Appendix I

Sequential Monitoring Plan

Sequential Monitoring Plan - Simulation

Efficacy and Futility boundaries were determined as presented in the sequential monitoring plan imbedded in the main protocol. Harm boundaries for the simulation were determined as the following:

- For the TBI cohort the harm boundary was determined as an observed survival difference between a given treatment and saline of -15%, -8%, and -3% at Looks 1, 2, and 3 respectively.
- For the Shock cohort the harm boundary was determined as an observed survival difference between a given treatment and saline of -20%, -13%, -10%, -8%, -5% and -3% at Looks 1, 2, 3, 4, 5 and 6 respectively.

Look 1:

Step 1: If the observed survival difference between a given treatment and saline crosses the harm boundary for a given agent, drop that agent and redistribute fluid stocks so that allocation is 1:1 for the remaining agent (Scenario 2). Stop the study if both agents cross the harm boundary.
Step 2: If the boundary for futility is crossed by one agent (or both agents), note that the boundary has been crossed. Drop the one agent (or stop the study) with the probability that the agent (or both agents) from the other study would also be futile. If just one agent is stopped for futility then redistribute fluid stocks so that allocation is 1:1 for the remaining agent (Scenario 2).
Step 2: If the superiority boundary is crossed by at least one agent, stop the study.
Step 3: If the study is not stopped, continue, with the appropriate allocations.

Looks after Look 1:

Scenario 1- Both agents:

Step 1: If the observed survival difference between a given treatment and saline crosses the harm boundary for a given agent, drop that agent and redistribute fluid stocks so that allocation is 1:1 for the remaining agent (Scenario 2). Stop the study if both agents cross the harm boundary.
Step 2: If the boundary for futility is crossed by one agent (or both agents), note that the boundary has been crossed. Drop the one agent (or stop the study) with the probability that the agent (or both agents) from the other study would also be futile. If just one agent is stopped for futility then redistribute fluid stocks so that allocation is 1:1 for the remaining agent (Scenario 2).
Step 3: If the superiority boundary is crossed by at least one agent, stop the study.
Step 4: If the study is not stopped, continue, with the appropriate allocations.

Scenario 2- One agent (which we designate H):

Step 1: If the observed survival difference for the agent crosses the harm boundary, stop the study.
Step 2: If the boundary for futility is crossed by the agent, note that the boundary has been crossed. Stop the study with the probability that the same agent from the other study would also be futile.
Step 3: If the superiority boundary is crossed by the agent, stop the study.
Step 4: If the study is not stopped, continue, with the appropriate allocations.

Detailed results of the simulation are presented in Tables A1 and A2 and the general results are imbedded in the main protocol.

Table A1: Cumulative % of 50,000 simulated trials that stop for efficacy for EITHER treatment, that stop for futility (or harm) of a SINGLE treatment, and that are still continuing for at least a single treatment at a given look and all previous looks for the TBI cohort for different treatment survival probabilities.

	Difference: $\theta_T - \theta_C$ [1]	-0.050	-0.030	-0.010	0.000	0.034	0.067
Look 1	% Efficacy [2]	0.00	0.00	0.00	0.01	0.09	0.88
	% Futile [3]	1.36	0.39	0.11	0.04	0.00	0.00
	% Trials at Look [4]	100.00	100.00	100.00	100.00	100.00	100.00
	CP for Non-Inferiority [5]	0.07	0.65	3.70	7.52	39.33	81.62
Look 2	% Efficacy	0.00	0.02	0.14	0.44	6.75	36.69
	% Futile	17.77	6.03	1.50	0.67	0.02	0.00
	% Trials at Look	99.85	99.98	100.00	99.99	99.91	99.12
	CP for Non-Inferiority	0.75	3.53	11.79	19.11	56.76	88.85
Final	% Efficacy	0.01	0.09	0.87	2.39	27.65	79.83
	% Futile	97.92	89.96	69.46	55.37	12.47	0.79
	% Trials at End	93.38	98.66	99.70	99.51	93.25	63.31

[1] θ_T Denotes the probability of survival with treatment and θ_c (= 0.646) denotes the probability of survival with saline.
[2] % Efficacy refers to the percentage of trials that are stopped for either treatment at a given look or preceding that look for efficacy.
[3] % Futile refers to the percentage of trials that a specific single treatment is stopped by a given look for futility
[4] % Trials refers to the percentage of trials that are being observed at a given look for at least one treatment.
[5] Conditional Power for the current look's futility boundary to observe Non-Inferiority for a specific treatment at the end of the study under the given difference $\theta_T - \theta_c$

Table A2: Cumulative % of 50,000 simulations that stop for efficacy for EITHER treatment, that stop for futility (or harm) of a SINGLE treatment, and that are still continuing for at least a single treatment at a given look and all previous looks for the SHOCK cohort for different treatment survival probabilities.

	Difference: $\theta_T - \theta_C$ [1]	-0.050	-0.030	-0.010	0.000	0.024	0.048
Look 1	% Efficacy [2]	0.00	0.00	0.00	0.00	0.00	0.00
	% Futile [3]	0.08	0.02	0.00	0.00	0.00	0.00
	% Trials at Look [4]	100.00	100.00	100.00	100.00	100.00	100.00
	CP for Non-Inferiority [5]	0.01	0.17	2.31	6.46	35.78	79.04
Look 2	% Efficacy	0.00	0.00	0.00	0.00	0.08	0.86
	% Futile	2.03	0.53	0.09	0.03	0.01	0.00
	% Trials at Look	100.00	100.00	100.00	100.00	100.00	100.00
	CP for Non-Inferiority	0.01	0.16	1.80	4.71	25.92	65.51
Look 3	% Efficacy	0.00	0.00	0.02	0.09	1.55	11.92
	% Futile	14.90	6.01	1.77	0.79	0.07	0.00
	% Trials at Look	99.84	99.97	100.00	100.00	99.92	99.14
	CP for Non-Inferiority	0.06	0.60	3.70	7.78	29.80	64.58
Look 4	% Efficacy	0.00	0.00	0.10	0.50	6.94	36.95
	% Futile	82.25	53.34	21.91	11.40	1.21	0.04
	% Trials at Look	96.69	99.26	99.88	99.88	98.45	88.08
	CP for Non-Inferiority	0.35	1.76	6.51	11.23	31.22	59.75
Look 5	% Efficacy	0.00	0.01	0.31	1.29	16.18	62.27
	% Futile	95.30	77.39	42.31	24.89	3.27	0.12
	% Trials at Look	29.02	64.57	90.93	96.11	92.94	63.05
	CP for Non-Inferiority	2.81	6.74	14.05	19.27	36.00	56.32
Final	% Efficacy	0.00	0.01	0.61	2.47	27.66	79.94
	% Futile	98.96	90.45	60.91	40.36	6.54	0.26
	% Trials at End	8.53	35.89	75.14	87.75	83.22	37.72

[1] θ_T Denotes the probability of survival with treatment and θ_c (= 0.510) denotes the probability of survival with saline.

[2] % Efficacy refers to the percentage of trials that are stopped for either treatment at a given look or preceding that look for efficacy.

[3] % Futile refers to the percentage of trials that a specific single treatment is stopped by a given look for futility

[4] % Trials refers to the percentage of trials that are being observed at a given look for at least one treatment.

[5] Conditional Power for the current look's futility boundary to observe Non-Inferiority for a specific treatment at the end of the study under the given difference $\theta_T - \theta_c$

Appendix J

Definitions of Tracked Infectious Complications, Non-Infectious Complications and SAE's

Definitions of Tracked Infectious Complications, Non-infectious Complications and SAE's

This document is intended to clarify definitions of infectious and non-infectious complications and potential SAE's which are tracked in the data collection forms, pursuant to analysis for secondary endpoints, observational analyses, and safety monitoring. Other potential study-related adverse events are defined in the protocol, including plans for reporting and monitoring such events.

Definitions for Nosocomial Infections tracked in the data collection forms

Bacteremia
To diagnose bacteremia then criteria #1 and #2 must be satisfied on the same day:
1. Recognized pathogen isolated on one blood culture or, if organism is a common skin contaminant two positive blood cultures are required.
2. At least one of the following: a. fever>38 C or hypothermia < 36 C, b. chills, c. hypotension (SBP< 90 mmHg)

Cholecystitis
Acute inflammation of the gallbladder as diagnosed by ultrasound.

Intra-abdominal abscess
To diagnose intra-abdominal abscess must meet both of the following criteria:
1. Intra-abdominal fluid collection requiring percutaneous or surgical drainage
2. Growth of bacteria on culture of the drainage fluid.

Line Infection
This refers to a central line infection and is diagnosed by either a positive line tip culture *or* the presence of pus and erythema at the central line insertion site.

Meningitis
Inflammation of the meninges, as diagnosed by lumbar puncture with positive cultures.

Pseudo-membranous colitis
A form of gastroenteritis which occurs when there is an over-growth of Clostridium difficile bacteria in the intestine, as evidenced by a stool culture positive for *C. difficile* toxin.

Pneumonia
To diagnose pneumonia all three criteria must be satisfied within a three-day period during days 1-28:
1. Radiological criteria (both a and b)
   a) new infiltrate corresponding in size to one segment or more of lung, or cavitation with an air fluid level
   b) radiographic finding persists ≥24 hrs.
2. Clinical criteria (both a and b)
   a) Fever (≥38.3 °C) or hypothermia (≤36.0 °C)
   b) WBC > 10 000/mm^3 **or** 25% increase over last available value **or** bands > 10% of total WBC **or** new decrease in WBC to < 4000/mm^3

3. Bacteriologic confirmation by **at least one of**:
    - positive blood culture for bacterial pathogen also identified in sputum or pathogenic bacteria (if not quantitative, then must be moderate or heavy growth)other respiratory culture
    - protected specimen brushing with ≥ 10^3 cfu/ml bacterial pathogen
    - BAL with >10^4 cfu/ml bacterial pathogen
    - positive gram stain from BAL fluid
    - positive sputum gram stain with ≥3+ of one type of bacteria
    - positive semi-quantitative sputum culture with ≥3+ growth of one type of pathogenic bacteria (if not quantitative, then must be moderate or heavy growth)

Urinary tract infection

To diagnose UTI must meet 1 & 2 on same day

1. Urine culture with >100,000 colonies of an organism
2. One of the following:
    a) Fever (≥38.3 °C) or hypothermia (≤36.0 °C)
    b) WBC >10 000/mm^3 or 25% increase over last available value or bands > 10% of total WBC or new decrease in WBC to < 4000/mm^3

Wound Infection

To diagnose wound infection must meet all the following criteria:

1. Erythema or wound drainage
2. One of the following:

a. fever (≥38.3 °C) **or** hypothermia (≤36.0 °C),
b. WBC > 10 000/mm^3 **or** 25% increase over last available value **or** bands > 10% of total WBC **or** new decrease in WBC to < 4000/mm^3

3. Intervention: wound drainage and/or treatment with antibiotics

Definitions for Non-infectious complications tracked in the Data Collection Forms

Abdominal Compartment syndrome
For the purposes of this study, a patient is considered to have abdominal compartment syndrome if they have a decompressive laparotomy.

Acute Lung Injury (ALI):
(a) Hypoxia with a PaO_2/FiO_2 ratio >200, ≤ 300 *and*
(b) bilateral infiltrates on chest X-ray *and*
(c) no clinical evidence of increased left atrial pressure or a pulmonary artery pressure of <18mmHg*

Acute Respiratory Distress Syndrome (ARDS):
Hypoxia with a PaO2/FiO2 ratio ≤200 *and*
(b) bilateral infiltrates on chest X-ray *and*
(c) no clinical evidence of increased left atrial pressure or a pulmonary artery pressure of <18mmHg*

**For those without pulmonary catheter monitoring clinical evidence of left atrial hypertension includes:*
a) Acute myocardial infarction ***or*** *known cardiomyopathy* ***or*** *severely reduced ejection fraction (<30%)* ***or*** *critical valvular disease*
b) chronic or acute oliguric renal failure with fluid input that exceeds output by ≥3 liters in the previous 24 hours

Cardiac arrest
The complete cessation of cardiac activity (heart beat) as documented in the chart.

Cerebral infarction
Infarction of brain tissue as documented by CT or MRI findings.

Deep venous thrombosis (DVT)
A blood clot that forms in a vein resulting in obstruction of venous flow, as documented by venous duplex testing.

Extremity compartment syndrome
Swelling of tissue within its anatomical enclosure (e.g. a leg or arm muscle within its muscular sheath) producing pressure that interferes with circulation and adversely affects the function and health of the tissue itself. For the purposes of this study a patient is considered to have extremity compartment syndrome if they have surgical decompression of the fascial compartments.

Fat embolism syndrome
Ultimately fat embolism syndrome is a clinical diagnosis of exclusion made by an attending or consulting physician and documented in the chart. This syndrome may include multiple signs and symptoms of varying subtlety (e.g. unexplained petechiae, unexplained hypoxia or difficulty ventilating, etc. usually occurring in the presence of a long bone fractures.)

Myocardial infarction
To diagnose myocardial infarction criteria one and two must be satisfied:
1) A typical rise and fall of biochemical indicators of myocardial necrosis. (Defined by the Joint European Society of Cardiology/ACC as "maximal concentration of troponin T or I exceeding the decision limit (99th percentile of the values for a reference control group) on at least one occasion during the first 24 hours after the index clinical event; or maximum value of CK-MB (preferably CK-MB mass) exceeding the 99th percentile of the values for a reference control group on 2 successive samples, or the maximal value exceeding twice the upper limit of normal for the specific institution on one occasion during the first hours after the index clinical event.")

AND at least one of the following:

2) a. Ischemic symptoms
   b. Development of pathologic Q's on ECG
   c. ECG changes indicative of ischemia (ST elevation or depression)
   d. Coronary intervention.

For the purposes of this study, a patient with non-specific ECG changes and elevated troponin (for whom the differential diagnosis includes acute coronary syndrome and blunt chest trauma) will be classified as an MI to ensure adequate review of potential complications.

Pulmonary embolus
A blood clot lodged in the lumen of a pulmonary artery as diagnosed by CT angiogram, pulmonary angiogram or ventilation perfusion scan.

Serious Adverse Events (SAE's)

A serious adverse event is any event that is fatal or immediately life threatening, is permanently disabling, or severely incapacitating, or prolongs inpatient hospitalization. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical, surgical intervention to prevent one of the outcomes listed above.

An unexpected event is any experience not identified by type, severity, or frequency in the current study protocol or an event that occurred unexpectedly in the course of treatment for blunt trauma or severe head injury. Adverse events will be considered to be study-related when the event follows a reasonable temporal sequence from administration of the study drug.

Anaphylaxis

A severe, whole body allergic reaction. Tissues in different parts of the body release histamine and other substances. This causes constriction of the airways, resulting in wheezing, difficulty breathing, and gastrointestinal symptoms such as abdominal pain, cramps, vomiting, and diarrhea.

Histamine causes the blood vessels to dilate (which lowers blood pressure) and fluid to leak from the bloodstream into the tissues (which lowers the blood volume). These effects result in shock. Fluid can leak into the alveoli (air sacs) of the lungs, causing pulmonary edema.

Hives and angioedema (hives on the lips, eyelids, throat, and/or tongue) often occur. Angioedema may be severe enough to block the airway. Prolonged anaphylaxis can cause heart arrhythmias.

Anaphylaxis can occur in response to any allergen. Common causes include insect bites/stings, horse serum (used in some vaccines), food allergies and drug allergies. Some people have an anaphylactic reaction with no identifiable cause.

Anaphylaxis occurs infrequently. However, it is life-threatening and can occur at any time. Risks include prior history of any type of allergic reaction. This should be reported as a serious adverse event.

Hypernatremia

Sodium >160 mEq/L requiring therapeutic intervention should be reported as a serious adverse event

Seizure
The physical manifestations (as convulsions, sensory disturbances, or loss of consciousness) resulting from abnormal electrical discharges in the brain (as in epilepsy). This should be reported as a serious adverse event.

Death unexplained by injury severity
Any death which is not explained by injury severity will be reported and reviewed. If it is not possible to exclude the possibility that the study protocol, in whole or in part, played a role in the death, then it will be reported as a serious adverse event.