Quality Improvement Guidelines for Transhepatic Arterial Chemoembolization, Embolization, and Chemotherapeutic Infusion for Hepatic Malignancy

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ABBREVIATION

HCC = hepatocellular carcinoma

PREAMBLE

The membership of the Society of Interventional Radiology (SIR) Standards of Practice Committee represents experts in a broad spectrum of interventional procedures from the private and academic sectors of medicine. Generally, Standards of Practice Committee members dedicate the vast majority of their professional time to performing interventional procedures; as such, they represent a valid broad expert constituency of the subject matter under consideration for standards production.

Technical documents specifying the exact consensus and literature review methodologies, as well as the institutional affiliations and professional credentials of the authors of this document, are available upon request from SIR, 3975 Fair Ridge Dr., Suite 400 N., Fairfax, VA 22033.

METHODOLOGY

SIR produces its Standards of Practice documents using the following process. Standards documents of relevance and timeliness are conceptualized by the Standards of Practice Committee members. A recognized expert is identified to serve as the principal author for the standard. Additional authors may be assigned depending on the magnitude of the project.

An in-depth literature search is performed with use of electronic medical literature databases. Then, a critical review of peer-reviewed articles is performed with regard to the study methodology, results, and conclusions. The qualitative weight of these articles is assembled into an evidence table, which is used to write the document such that it contains evidence-based data with respect to content, rates, and thresholds.

When the evidence of literature is weak, conflicting, or contradictory, consensus for the parameter is reached by a minimum of 12 Standards of Practice Committee members by using a modified Delphi Consensus Method (Appendix A). For the purposes of these documents, consensus is defined as 80% Delphi participant agreement on a value or parameter.

The draft document is critically reviewed by the Standards of Practice Committee members by telephone conference calling or face-to-face meeting. The finalized draft from the Committee is sent to the SIR membership for further input/criticism during a 30-day comment period. These comments are discussed by the Standards of Practice Committee, and appropriate revisions made to create the finished standards document. Before its publication, the document is endorsed by the SIR Executive Council.

INTRODUCTION

Intraarterial therapy for a variety of hepatic malignancies represents an important therapeutic procedure in individuals with liver-dominant neoplasms. Such tumors include primary hepatic malignancies and certain other cancers in which the liver is the dominant site of disease. A variety of different cancers are amenable to treatment (1–4). Success with chemoembolization and embolization has been reported with the majority of reports focusing on chemoembolization. Nearly 500,000 patients worldwide are diagnosed with hepatocellular carcinoma (HCC) annually, and the incidence in the United States is increasing dramatically (5,6). Most patients with HCC are not surgical candidates at the time of referral to interventional radiology. External-beam radiation therapy is ineffective, and stereotactic radiation therapy remains experimental, with fewer cumulative data than chemoembolization (7). Targeted therapies such as sorafenib (Nexavar), although statistically superior to supportive care, have shown limited effectiveness in the treatment of HCC (8). Systemic regimens remain ineffective at prolonging survival (9). Transplantation remains the best curative option for HCC. The demand for donated organs continues to outstrip supply (10). Many patients require some kind of image-guided therapy as a bridge to transplantation or as palliative therapy (11).

The liver is the dominant site of metastatic disease for a number of malignancies, including colorectal carcinoma, neuroendocrine tumors, and

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metastatic uveal melanoma. Fewer than 20% of patients with metastatic colorectal carcinoma are candidates for curative surgical resection (12). Advances in systemic and biologic therapies have provided significant improvement in survival with colorectal metastases, but these therapies have limited benefit for the majority of patients with metastatic neuroendocrine tumors (13–16). Nonsurgical candidates often have diffuse disease. Chemoembolization, and embolization (for neuroendocrine tumors), can play an important role in the treatment of these patients, particularly when primary systemic regimens have failed.

These guidelines are written to be used in quality improvement programs to assess chemoembolization. The most important processes of care are (i) patient selection, (ii) performing the procedure, and (iii) monitoring the patient. The outcome measures or indicators for these processes are indications, success rates, and complication rates. Outcome measures are assigned threshold levels.

DEFINITIONS

Chemoembolization refers to treatment with a mixture of chemotherapy and embolic agents, typically as oily chemoembolization or drug-eluting bead chemoembolization.

- *Oily chemoembolization* is defined as the infusion of a mixture of chemotherapeutic agents with ethiodized oil (Ethiodol; Guerbet, Villepinte, France) followed by embolization with particles such as calibrated microspheres, polyvinyl alcohol, or Gelfoam (absorbable gelatin sponge).
- *Drug-eluting bead chemoembolization* is defined as the infusion of calibrated microspheres that are designed to bond with chemotherapeutic agents and release the drugs over time following treatment.
- *Embolization* is defined as blockade of hepatic arterial flow with particles alone (typically calibrated microspheres, polyvinyl alcohol, or Gelfoam).
- *Immunoembolization* refers to infusion of granulocyte macrophage-colony stimulating factor with Ethiodol and Gelfoam.
- *Hepatic artery chemotherapeutic infusion* is defined as injection of chemotherapy with or without ethiodized oil in the hepatic artery without embolization.
- *Liver-dominant neoplasm* is defined as a malignancy in which the hepatic component is the only site of disease or is the site of disease most likely to lead to patient morbidity and/or mortality.
- *Image-guided therapy* refers to the use of fluoroscopy, digital subtraction angiography, C-arm computed tomography (CT), CT, ultrasound (US), or magnetic resonance (MR) imaging to target and monitor treatment of tumors for therapy. In the liver, this is accomplished by catheter-based means (as outlined earlier) or by percutaneous tumor ablation (17).
- *Tumor ablation* is defined as the direct application of chemical or thermal therapies to a specific focal tumor (or tumors) in an attempt to achieve eradication or substantial tumor destruction. Tumor ablation methods fall into one of three main categories: chemical, thermal, or biomechanical (17).
- *Chemical ablation* refers to instillation of a pharmacologic agent to cause tumor necrosis. Examples of chemical agents include absolute ethanol and acetic acid.
- *Thermal ablation* refers to application of energy to cause tumor necrosis. Examples of energy sources include radiofrequency, laser, microwave, US, and cryotherapy.
- *Biomechanical ablation* refers to application of energy to lead to cell breakdown. The primary example is irreversible electroporation.

Chemoembolization, embolization, and chemotherapeutic infusion are performed after catheterization of the proper, lobar, segmental, or subsegmental hepatic arteries by using standard angiographic principles as described in the SIR quality improvement guidelines for diagnostic angiography (18). Unless otherwise stated, references in this document will specifically refer to oily chemoembolization, as the majority of the existing literature has used this technique.

Although practicing physicians should strive to achieve perfect outcomes (eg, 100% success, 0% complications), in practice all physicians will fall short of this ideal to a variable extent. Thus indicator thresholds may be used to assess the efficacy of ongoing quality improvement programs. For the purposes of these guidelines, a threshold is a specific level of an indicator which should prompt a review. "Procedure thresholds" or "overall thresholds" reference a group of indicators for a procedure, eg, major complications. Individual complications may also be associated with complication-specific thresholds. When measures such as indications or success rates fall below a (minimum) threshold, or when complication rates exceed a (maximum) threshold, a review should be performed to determine causes and to implement changes, if necessary. For example, if the incidence of abscess formation is one measure of the quality of chemoembolization, values in excess of the defined threshold (in this case, 2%) should trigger a review of policies and procedures within the department to determine the causes and to implement changes to lower the incidence of the complication. Thresholds may vary from those listed here; for example, patient referral patterns and selection factors may dictate a different threshold value for a particular indicator at a particular institution. Therefore, setting universal thresholds is very difficult, and each department is urged to alter the thresholds as needed to higher or lower values to meet its own quality improvement program needs.

Complication stratification in interventional radiology is currently undergoing revision, but, to date, has been performed on the basis of procedural outcomes. Major complications result in admission to a hospital for therapy (for outpatient procedures), an unplanned increase in the level of care, prolonged hospitalization, permanent adverse sequelae, or death. Minor complications result in no sequelae; they may require nominal therapy or a short hospital stay for observation (generally overnight; Appendix B). The complication rates and thresholds listed herein refer to major complications.

INDICATIONS

General Indications

Chemoembolization is indicated in patients with liver-dominant hepatic malignancies who are not candidates for curative resection. All patients should undergo preprocedural imaging evaluation including some combination of contrast-enhanced CT, MR imaging, and/or positron emission tomography/CT to ensure that disease is liver-dominant. Although limited treatment is possible in the setting of portal vein thrombosis, outcomes are optimized in the setting of a patent portal vein or with hepatopetal flow via collateral vessels (19–21). If there is a question of adequate portal perfusion at cross-sectional imaging, confirmation can be obtained at catheter angiography immediately preceding chemoembolization. Patient performance status should be determined during the preliminary interventional radiology clinic visit. Preprocedural evaluation also includes laboratory evaluation including complete blood count, prothrombin time, and evaluation of liver and kidney function. Exclusion criteria based on laboratory values are not definitively established. However, the constellation of more than 50% liver replacement with tumor, bilirubin level greater than 2 mg/dL, lactate dehydrogenase level greater than 425 mg/dL, and aspartate aminotransferase level greater than 100 IU/L has a strong anecdotal association with increased postprocedural mortality (22). Individual abnormalities of these four parameters have not been shown to predict adverse outcome from chemoembolization (23). Laboratory values and scoring systems have been used differently by other authors. Commonly used scoring systems are outlined in **Tables 1–3**. A bilirubin cutoff value of 3 mg/dL has been described (24). The Child-Pugh scoring system is superior to the Model for End-stage Liver Disease system at predicting long-term survival in HCC (23). Patients with Child-Pugh class A disease or class B disease with an albumin level of at least 3.4 g/dL have improved survival. Another group (25) found that Model for End-stage Liver Disease scores greater than 10 and Cancer of the Liver Italian Program scores greater than 2 were negative predictors of survival. The optimal scoring system to predict survival following therapy remains undefined, and investigation of novel predictors of outcome continues (26–28).

Hepatocellular Carcinoma. Secondary to underlying cirrhosis, fewer than 20% of patients are candidates for surgical resection (9). Transplantation remains the only curative option for patients with HCC, and indi-

Table 1. Child-Pugh Scoring System

Variable	1	2	3
Encephalopathy	None	Moderate	Severe
Ascites	None	Moderate	Severe
Bilirubin (mg/dL)	< 2	2–3	> 3
Albumin (g/dL)	> 3.5	2.8–3.4	< 2.8
Prothrombin time (s)	< 14	15–17	> 18

Note.—A score of 5–6 represents Child-Pugh class A disease, 7–9 represents class B disease, and 10–15 represents class C disease.

Table 2. Model for End-Stage Liver Disease Scoring System

R = 0.957 × loge (creatinine [mg/dL)] + 0.378 × loge (bilirubin [mg/dL]) + 1.12 × loge (INR) + 0.643 × (cause of cirrhosis [0 for alcohol-induced cirrhosis, 1 for non–alcohol-induced cirrhosis])

Note.—INR = International Normalized Ratio.

viduals with limited disease (ie, one tumor < 5 cm or three tumors < 3 cm each) should be evaluated for transplantation during workup as part of a multidisciplinary effort. In potential transplant recipients, chemoembolization may decrease the drop-off rate from the transplant list and limit recurrence when a new organ has been obtained (29,30). Chemoembolization is being investigated for intrahepatic recurrence following transplantation as well (31). In limited experience, chemoembolization has been found to be effective in management of larger tumors and as adjuvant therapy for HCC resection (32,33).

Initial randomized trials evaluating chemoembolization versus symptomatic treatment had disappointing results (34–37). However, three well constructed randomized trials (1,2,38) have demonstrated significantly improved survival with chemoembolization. Poor outcomes from the initial trials can be directly linked to treatment of patients with advanced disease and to administration of excessive therapy (39). These outcomes reinforce the need to treat patients with well compensated cirrhosis and to repeat therapy in the setting of viable tumor on follow-up cross-sectional imaging (40). Many patients whose disease is treatable with chemoembolization may also be treatable with yttrium-90 as well (41). Patients with small tumors may also be considered for percutaneous ablative therapies, alone or in combination with chemoembolization (42–44). The choice between therapies should be based on the overall size, number, and location of the tumors.

Embolization for HCC has been demonstrated to be effective (45,46). Trials of drug-eluting beads loaded with doxorubicin and other agents are emerging (47–50). In a prospective, multicenter, randomized trial with a primary endpoint of tumor response at 6 months from treatment (47), there was not a statistical difference between drug-eluting beads and oily chemoembolization. However, patients with limited hepatic reserve or performance status showed better outcomes with drug-eluting beads compared with chemoembolization. In a single-center prospective randomized trial (48), treatment with drug-eluting beads loaded with doxorubicin resulted in a statistically longer time to progression than bland embolization.

Neuroendocrine Malignancy. Initial control of symptoms is usually performed with short- or long-acting somatostatin agents. Most patients with symptomatic disease from hormone production or bulk have diffuse metastases, a contraindication to surgery. The frequent presence of diffuse metastases also limits the number of patients who are candidates for percutaneous ablative therapies. Chemoembolization and embolization of patients with hepatic metastases from neuroendocrine tumors can result in durable elimination of hormonal symptoms (3,51). A number of patients with hormonally active liver metastases also have extrahepatic disease at the time of diagnosis. However, as treatment can still reduce or eliminate symptoms, treatment should not be withheld from these patients (52,53). Published experience with drug-eluting beads for this disease entity remains preliminary (54,55). Early results appear similar to those of other transarterial therapies.

Colorectal Carcinoma. Fewer than 20% of patients with colorectal metastases are candidates for curative resection (12). Survival rates with systemic chemotherapy have improved, with mean survival approaching 2 years (13). Chemoembolization can provide palliation and is typically used as a salvage option following systemic therapy. There is evidence that patient survival is improved if patients have had one or two lines of therapy versus three or more (56). Preliminary data with drug-eluting beads have been accrued in registry format (57). Further validation of this technique is pending.

Metastatic Uveal Melanoma. Metastatic uveal melanoma is rarely resectable, and a significant number of patients die of liver failure secondary to hepatic metastases. The optimal treatment is by immunoembolization, with other intraarterial regimens rarely achieving survival times exceeding 9–10 months (58–61).

Other Metastases. Other tumors that may present with liver-dominant metastases include breast carcinoma and soft-tissue sarcomas, including gastrointestinal stromal tumors. These tumors have been successfully treated with chemoembolization or embolization. Patient survival appears to be improved compared with historical controls, although randomized prospective data are not available (62–64).

Participation by the radiologist in patient follow-up, both in the hospital and at imaging follow-up, is an integral part of chemoembolization and will limit the incidence of postprocedural complications and ensure appropriate scheduling of follow-up therapy. Close follow-up with monitoring and management of the patient by the interventional radiologist is appropriate.

The indication for intraarterial treatment of hepatic malignancy is the presence of liver-dominant malignancy with adequately preserved hepatic function. The threshold for this indication is 95%. When fewer than 95% of procedures are for this indication, the department will review the process of patient selection.

Preprocedural Considerations

Hydration is essential with intravenous administration of 150–300 mL/h of normal saline solution. Other premedications include antiemetic agents and steroids. Many operators administer antibiotic coverage for Gram-negative enteric organisms, although this practice is not universal or prospectively proven to be beneficial for all patients (65,66). In patients without an intact sphincter of Oddi from previous surgery, sphincterotomy, or biliary drainage, the risk of infection following embolization is significantly increased. The risk of postembolization infection appears to be reduced by prolonged pre- and posttreatment antibiotic therapy (67,68). The need for pretreatment bowel preparation is not definitive (69). In patients with carcinoid tumors, pretreatment with subcutaneous octreotide is important to limit carcinoid crisis caused by hormonal dumping from tumor necrosis after embolization (3).

Procedural Considerations

Given the frequency of variant hepatic arterial anatomy, initial angiography should include a study of the superior mesenteric and celiac arteries (70). Filming should be performed through the portal venous phase to ensure no change in the patency of the portal venous structures from preprocedure imaging. Practice patterns for level of catheter selection range from subsegmental to lobar embolization, depending on the type and number of tumors to be treated as well as the philosophy of the individual doing the procedure. Treatment of the entire liver in one session is associated with an increase in mortality (51). When treatment has led to

Table 3. Cancer of the Liver Italian Program Scoring System

Variable	0 Points	1 Point	2 Points
Child-Pugh class	A	B	C
Tumor morphology	Uninodular	Multinodular	Massive/> 50% of liver
α-Fetoprotein (ng/mL)	< 400	> 400	NA
Macrovascular invasion	No	Yes	Yes

Note.—NA = not applicable.

permanent occlusion of the native hepatic arteries, several collateral pathways have been treated with clinical success, including the inferior phrenic, internal mammary, and intercostal arteries (71–74). If these collateral arteries have potential communication with cutaneous vessels, embolization should be performed to limit the risk of cutaneous ischemic ulceration (75). Treatment should avoid the cystic artery if possible. If treatment of the tumor is not feasible without including the cystic artery in the infused area, chemoembolization may still be performed. The principal risk of treatment of the cystic artery is pain, which may potentially lengthen the posttreatment hospital stay but does not result in significant risk to the gallbladder itself (76). Intermittent infusion of 1% lidocaine between aliquots of the chemotherapy/Ethiodol slurry decreases postembolization pain (77,78).

Oily Chemoembolization versus Embolization. Randomized trials for treatment of HCC comparing protocols with and without chemotherapy are limited. A prospective randomized trial with three arms comparing survival with chemoembolization versus embolization versus symptomatic treatment (2) showed a significant survival benefit for chemoembolization versus symptomatic treatment, and the trial was halted. At the time the trial was terminated, embolization without chemotherapy had shown similar survival to that associated with chemoembolization. The trial was not continued to determine whether embolization without chemotherapy would lead to a survival benefit versus symptomatic treatment alone. A separate metaanalysis did not reveal any clear-cut benefit from the addition of chemotherapy to embolization (79). A complicating factor in determining the gold-standard arterial infusion therapy is that chemotherapy regimens vary significantly from trial to trial. No ideal chemotherapeutic agent has been identified. A definitive statement regarding treatment with or without chemotherapy cannot be made without an adequately powered prospective trial.

Oily Chemoembolization versus Chemotherapeutic Infusion. Few comparisons of oily chemoembolization versus chemotherapeutic infusion techniques are available. Infusion without embolization appears to result in a lower percentage of tumor necrosis compared with chemoembolization, particularly in HCC greater than 3 cm in diameter (80). However, toxicity to the surrounding liver may be lower with infusion alone (81). Chemotherapeutic infusion may be considered an option in patients with severe hepatic dysfunction.

Postprocedural Considerations

Many practitioners recommend antibiotic treatment for 3–7 days following chemoembolization to cover Gram-negative enteric pathogens. Data regarding the need for routine antibiotic prophylaxis are mixed, without evidence of benefit (66). If a patient has a disrupted sphincter of Oddi, antibiotic treatment should be continued for approximately 2 weeks (67,69,82). Even with extended administration of antibiotics, data for this group of patients are limited, and the operator should proceed with caution in the setting of any biliary abnormality. Antibiotic treatment may be converted to oral administration as soon as patients can tolerate a normal diet, in order to facilitate expedient discharge. Ondansetron should be continued as long as needed. Narcotic agents should be available. One method preferred by many interventionalists to control pain is to administer narcotic agents via a patient-controlled analgesia pump.

Postprocedural Imaging. Follow-up imaging should be performed 4–6 weeks after all tumor-bearing areas have been treated. If treatment of both lobes of the liver is planned, imaging between sessions may be performed based on operator preference. Signs of tumor necrosis on CT include ethiodized oil uptake and absence of arterial-phase enhancement when it was present before chemoembolization (83,84). Absent arterial enhancement when it was present before therapy is the principal determinant of tumor necrosis on MR imaging (85). There is a paucity of literature regarding postchemoembolization follow-up of lesions without arterial phase enhancement. Gross enlargement of a lesion or nodular enhancement in portal vein or delayed-phase imaging has been described as evidence of residual or recurrent tumor following radiofrequency ablation of lesions without initial arterial-phase enhancement (86). Similar findings may be present in the setting of residual or recurrent tumor following chemoembolization. Patients without active disease at follow-up should undergo follow-up imaging every 3–4 months.

Repeat Treatment. Individuals with HCC or metastases from nonneuroendocrine tumors require further treatment when new or residual disease is detected (40). Patients with liver metastases from symptomatic neuroendocrine tumors should be treated again if the initial treatment does not result in symptomatic improvement or when symptoms recur. Before additional chemoembolization sessions, liver function test results and complete blood count should be rechecked to ensure the patient is still an appropriate candidate.

Success Rates

Technical Success. Successful chemoembolization is defined as successful catheter placement and administration of selected agents. The threshold for technical success of chemoembolization is 98%.

Clinical Success. Clinical success is defined as successful tumor necrosis resulting in effective palliation. Effective palliation is tumor-dependent, with survival as the primary outcome for tumors such as HCC and colorectal carcinoma. To reach this success, individual operators should have survival rates comparable to those in the established literature. Thresholds are set less than 100%, as operators will encounter patients in practice who require therapy whose clinical presentations are worse than allowed in clinical trials. In patients with symptomatic neuroendocrine malignancy, clinical success is defined as the elimination of hormonal symptoms (**Table 4**) (3,23,33,38,45,46,52,53,56,58,59,63,87–98).

COMPLICATIONS

Complications occur in approximately 10% of patients. Use of drug eluting beads is relatively new and toxicities related to this technique are evolving. Published complication rates and suggested thresholds include those in **Table 5** (45,67–69,99–103).

Postembolization syndrome (fever, pain, increased white blood cell count) by itself is not considered a complication but an expected outcome of embolotherapy (76). As noted earlier, a small percentage of patients will

Table 4. Thresholds for Median Survival for Various Tumor Pathologies (3,23,33,38,45,46,52,53,56,58,59,63,87–98)

Lesion	Median Survival (mo)	References	Threshold (%)
Hepatocellular carcinoma	20	23,33,38,45,46,87–89	50
Colorectal carcinoma	10	56,90–95	50
Neuroendocrine tumors	26	3,52,53,96,97	50
Ocular melanoma	11	58,59	50
Metastatic sarcoma	19	63,98	50

Table 5. Specific Major Complications for Hepatic Arterial Chemoembolization (45,67–69,99–103)

Complication	Reported Rate (%)	Suggested Threshold (%), Sources
Liver failure	2.3	4 (45)
Abscess with functional sphincter of Oddi	1–2	2 (99–101)
Postembolization syndrome requiring extended stay or readmission	4.6	10 (45)
Abscess with biliary–enteric anastomosis/biliary stent/sphincterotomy with premedication	0–15	10 (67–69)
Surgical cholecystitis	< 1	1 (99,102,103)
Biloma requiring percutaneous drainage	< 1	2 (102)
Pulmonary arterial oil embolus	< 1	1 (103)
Gastrointestinal hemorrhage/ulceration	< 1	1 (103)
Iatrogenic dissection preventing treatment	< 1	1 (102)
Death within 30 d	2–4	4 (102,103)

have prolonged symptoms requiring a greater level of postprocedure care (45). Published rates for individual types of complications are highly dependent on patient selection and are based on series comprising several hundred patients, which is a volume larger than most individual practitioners are likely to treat. Therefore, we recommend that complication-specific thresholds should usually be set higher than the complication-specific reported rates listed here. It is also recognized that a single complication can cause a rate to cross above a complication-specific threshold when the complication occurs in a small volume of patients, eg, early in a quality improvement program. In this situation, the overall procedure threshold is more appropriate for use in a quality improvement program.

In **Table 5**, all values are supported by the weight of literature evidence and panel consensus.

OVERALL PROCEDURE THRESHOLD

The threshold is 15% for all major complications resulting from hepatic arterial chemoembolization, embolization, or chemotherapeutic infusion.

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APPENDIX: A: CONSENSUS METHODOLOGY

Reported complication-specific rates in some cases reflect the aggregate of major and minor complications. Thresholds are derived from critical evaluation of the literature, evaluation of empirical data from Standards of Practice Committee members' practices, and, when available, the SIR HI-IQ System national database.

Consensus on statements in this document was obtained with use of a modified Delphi technique (1,2).

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APPENDIX: B: SOCIETY OF INTERVENTIONAL RADIOLOGY STANDARDS OF PRACTICE COMMITTEE CLASSIFICATION OF COMPLICATIONS BY OUTCOME

Minor Complications

A. No therapy, no consequence.

B. Nominal therapy, no consequence; includes overnight admission for observation only.

Major Complications

C. Require therapy, minor hospitalization ($\geq$ 24 h but $<$ 48 h).

D. Require major therapy, unplanned increase in level of care, prolonged hospitalization ($>$ 48 h).

E. Result in permanent adverse sequelae.

F. Result in death.