Monoclonal Antibodies Infusion Reactions:
Etiology, Prediction and Management by Nurse Practitioners

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A master's project submitted in partial fulfillment
of the requirements for the degree of

MASTERS OF NURSING

WASHINGTON STATE UNIVERSITY- YAKIMA, WA
College of Nursing
May 2012
To the Faculty of Washington State University:

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Monoclonal Antibodies Infusion Reactions:
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Abstract

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May 2012

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Submitting to the Clinical Journal of Oncology Nursing: Etiology, Prediction and Management of Monoclonal Antibodies Infusion Reactions.

Monoclonal antibodies have an increased risk of infusion reaction. Factors in the etiology of infusion reactions include percentage of mouse protein; immune response and cytokine release. Reactions typically occur with the initial infusion and in the presence higher tumor burdens. Predictive factors of infusion reactions include prior first infusions, increased amounts of lymphocytes, geographical region and rapid infusions. Management of reactions includes consideration of a test dose, premedication, supportive care and treatment alternatives of fully humanized monoclonal antibodies. Additional management options include desensitization protocols, as well as standing orders and crash cart availability.

To improve patient safety, an emphasis is needed on staff education and the development of a process to evaluate and identify patients at risk. Standardized clinical pathways, policies and procedures need to be well rehearsed by staff to reduce
negative consequences of infusion reactions. More research is needed on the identification of risk factors, as well as a clearer understanding of the mechanism of a monoclonal antibody infusion reaction. Monetary implications and hospitalizations are important to further determine the direct cost of infusion reactions of monoclonal antibodies.

*Keywords:* monoclonal antibodies, infusion reactions, oncology, adults
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Monoclonal Antibodies Infusion Reactions: Etiology, Prediction, and Management

**Statement of the Problem**

Monoclonal antibodies are biologic agents approved by the Food and Drug Administration for oncology treatment. Rituximab was the first monoclonal antibody developed and used for the treatment of follicular lymphoma in 1997 (Chung, 2008). Vogel (2010) defined monoclonal antibodies as antibodies secreted by a B-lymphocyte, designed to recognize specific protein markers (antigens) on the surface of a foreign cell and create an immune response marking the cell for destruction. Monoclonal antibodies are engineered with two binding arms, one binding to the tumor cell and the other binding to the effector cell, creating antibody mediated cell kill referred to as targeted therapy (Harris, 2004). Targeted therapy triggers the immune system to activate the complement system causing cell lysis and programmed cell death (Harris 2004). Many monoclonal antibodies have been developed, approved and used for a variety of cancers. Rituximab is a monoclonal antibody consisting of 34% mouse protein; new scientific developments have created humanized variations of monoclonal antibodies with 10% mouse protein and xenomouse variants (genetically engineered mouse protein) with 100% human protein (Kang, 2007). The percentage of mouse protein is a causal factor in immunogenic responses, including infusion reaction (Kang, 2007).

When any infusional agent is injected into a person’s venous system, there is always a risk of reaction. Infusion reactions are defined as symptoms associated with a complex of chills, fever, nausea, asthenia, headache, skin rash, pruritus or severe
hypersensitivity reaction characterized by bronchospasm, hypotension, urticaria or cardiac arrest (Chung, 2008). The typical infusion reaction is a type I hypersensitivity reaction caused by a release of immune modulators and inflammatory cytokines (Siena et al., 2010). A type I reaction is characterized as an activation of IgE (immunoglobulin E) causing an immediate allergic reaction. IgE is the antibody produced by plasma cells during allergen exposure (Banasik, 2009). A type I reaction typically occurs after a previous exposure to an allergen creating a higher level of IgE in the blood system to activate a hypersensitivity response (Banasik, 2009). Cytokines promote inflammation and encourage the activation of white blood cells, playing an important role in the immune response and creating intercellular communication in the body’s immune system (Banasik, 2009).

The question can be asked, “How can oncology nurse practitioners predict and manage infusion reactions from monoclonal antibodies to diminish the clinical consequences of these reactions?” A nurse practitioner is defined as a registered nurse with advanced education that assumes primary responsibility for continuous and comprehensive management of a broad range of patients (Washington State Legislature, 2011). The purposes of this paper are to examine the evidence for (a) factors that cause oncologic monoclonal antibody infusion reactions, (b) factors that predict reactions, and (c) best practices for the management of reactions by nurse practitioners.
Search Strategies

Google Scholar through the WSU library website was utilized using research key words, "monoclonal antibodies," "infusion reactions," "oncology," and "adults." Four hundred thirty-six articles were found, of which twenty-five were reviewed and eight were chosen. Pubmed was employed for a second search using key words of "infusion reactions with monoclonal antibodies" and "adult cancer treatment." Fifty-one articles were found, twenty were reviewed and eight were chosen. Articles consisted of chart reviews, research studies, meta-analysis and literature reviews. The sixteen chosen articles were organized into three sections: factors that cause reactions to monoclonal antibodies (three articles), factors that predict infusion reactions (six articles) and management of infusion reactions (seven articles). All the articles were chosen due to their subject matter, appropriateness to this literature review and availability. In addition to the literature review, several websites were also utilized to assist in the definition of the nurse practitioner role, to search for a theoretical framework and to contribute to the understanding of the engineering of the monoclonal antibodies.

Theoretical Framework

The model of symptom management is a conceptual framework developed by Marylin Dodd and colleagues at the University of California, San Francisco School of Nursing symptom management group (http://nurseweb.ucsf.edu/www/rcsm.htm). It is a deductive middle-range theory (Linder, 2010). The overarching concepts that encircle the model include person, environment, and health/illness (see Figure 1). Within these circles, three dimensions are identified: symptom experience, symptom management
strategies and symptom outcomes. The premise is that all three of these dimensions are interrelated and need to be considered when examining symptom management (Larson et al., 1994). The model depicts the inter-relationships among the three symptom dimensions with bidirectional arrows.

Symptom management is a dynamic process that changes due to patients responses (Larson et al., 1994). The model accounts for the patient, family, health care system and health care provider along with the perception, evaluation, and health outcomes to symptom management (Larson et al., 1994). For the purpose of this paper an acute infusion reaction is a side-effect symptom of a monoclonal antibody infusion. The symptom management model proposes that a symptom is a subjective experience that changes a person’s biopsychosocial functioning, sensation and or cognition (Larson et al., 1994).

Literature Review

The literature review is organized into three sections based on the final categorization of the fifteen articles selected at the conclusion of the literature search. Each section is now described and a table summarizes the review (see Table 1).

Factors that Cause Infusion Reactions

Vogel (2010) performed a meta-analysis focusing on the etiology of infusion reactions, using rituximab as the example. The body’s immune system responds to any foreign agent causing a reaction that can be mild to hypersensitive. These responses are a result of a B lymphocytes and T lymphocytes recognizing an antigen on foreign cells, eliciting an immune response and destroying the cell (Vogel, 2010). Monoclonal
antibodies are a clone of a B lymphocyte designed to target specific tumor antigens. When cells are destroyed, cytokines are released, creating infusion reactions similar to a type I hypersensitivity reaction typically occurring with the first infusion and or a higher tumor burden (Vogel 2010).

Kang and Saif (2007) conducted a literature review consisting of a description of the construction of monoclonal antibodies and the percentage of mouse protein that results in immunological responses. Reaction to the different monoclonal antibodies is not clearly understood; however, there is a correlation between percentage of mouse protein and percentage of overall incidence of infusion reaction (Kang & Saif, 2007). Infusion reaction pathophysiology is not completely understood or described in the literature, but it seems to be partially due to cytokine release or have an IgE (immunoglobulin E) mediated component (Kang & Saif, 2007).

Patel, Archie and Goldberg (2006) explained through a meta-analysis that monoclonal antibodies are derived from mice proteins that form human anti-mouse antibodies that are substantially immunogenic. The development of three variations of monoclonal antibodies-- chimeric, humanized, human-- decreases the percentage of mice protein, resulting in a lower immunogenic response (Patel, Archie & Goldberg, 2006). Although the true etiology of infusion reactions is still unclear, the literature supports the premise that reactions are not IgE mediated. Evidence indicates the majority of reactions occur with first infusions. One plausible hypothesis for first infusion reactions could be the exposure to the murine (mouse) protein in urban settings that causes sensitivity (Patel et al., 2006).
Factors that Predict Infusion Reactions

Chung (2008) conducted a literature review summarizing that, even though infusion reactions vary with monoclonal antibodies, reactions predominantly occur with the first infusion. Severity of infusion reactions has a direct correlation with the amount of lymphocytes, i.e., the greater the amount of circulating lymphocytes, the higher the risk and severity of the infusion reaction (Chung, 2008). The presence of C-IgE (anti-cetuximab immunoglobulin E, an IgE that cross-reacts with a monoclonal antibody cetuximab), results in a higher rate of infusion reaction (Chung, 2008).

The presence of C-IgE is geographically distributed (Chung, 2008). O’Neil et al. (2007) conducted a retrospective chart review (N=88) showing a 20% higher hypersensitivity rate to cetuximab in Tennessee and North Carolina, compared to less than 3% nationally. This finding suggested a pre-existing immunoglobulin E-based immune reaction to cetuximab. O’Neil and colleagues (2007) speculated a cross-reactive response in this region of the United States was caused by prior exposure to mouse antigen or another antigen that mimics cetuximab.

Reidy et al. (2007) examined the infusion length time of the monoclonal antibody bevacizumab in a sample of 1,077 persons at a 5mg/kg dose. The authors’ discussed how infusion lengths are established empirically before a phase 1 clinical trial begins, typically based on laboratory data, logical considerations or pragmatically based information (Reidy et al., 2007). The study concluded that the rate of infusion did not contribute to an increased rate of infusion reactions, recommending a standardized infusion rate of 0.5mg/kg/minute (Reidy et al., 2007).
Tuthill, Crook, Corbet, King and Webb (2009) examined infusion rates of rituximab (chimeric monoclonal antibody with 34% mouse protein). Initial infusion rates of rituximab were typically six hours in length with subsequent infusions given over four hours. The results found no infusion reactions in the 54 participants enrolled in the study. The initial infusion of four hours was followed by rapid infusion of one hour on the second and subsequent infusions (Tuthill, Crook, Corbet, King & Webb, 2009). It was concluded that the absence of infusion reactions following a rapid administration time of sixty minutes suggested safe administration with greater patient satisfaction (Tuthill et al., 2009).

A case report by Zahrani, Ibrahim and Eid (2009) also examined the rate of infusions of monoclonal antibodies, specifically rituximab. A small sample (N=21) tolerated a rapid administration with only three mild infusion reactions, one with nasal congestion, one with abdominal pain and one with facial itchiness and redness. The investigators’ concluded that the rate of infusion did not contribute to an increase in infusion reactions (Zahrani, Ibrahim & Eid, 2009).

Schwartzberg et al. (2009) investigated the implications of infusion reactions for the patient, caregiver and clinical practice. Although the study’s intent was to examine the impact of infusion reactions on staff time, resources and cost, additional information was examined for infusion reactions. Of the 165 participants, fifty-eight (35%) experienced reactions during infusions ranging from mild to severe. The 48 mild reactions consisted of flushing, itching, nausea and vomiting, hypotension, chills and rigors, muscle aches and rhinitis (Schwartzberg et al., 2009). The 10 severe reactions included difficulty breathing, nausea and vomiting and hypotension (Schwartzberg et al.,
2009). These reactions resulted in an increase in time spent in the outpatient clinic, diminishing any advantage gained by a shorter infusion time (Schwartzberg et al., 2009).

**Management of Infusion Reactions**

George et al. (2010) conducted research using a retrospective cohort design to document the management of infusion reactions in patients receiving cetuximab. The research discovered that administration of a small test dose of cetuximab under observation was a factor that influences patient safety, staff efficiency and financial resources, resulting in an 87% cost saving (George et al., 2010). The authors' recommended including premedication of both intravenous corticosteroid and an H1 antagonist prophylactically; they also suggested using panitumumab (fully humanized monoclonal antibody) in cases of colorectal cancer (George et al., 2010).

Siena et al. (2010) performed a post-hoc analysis of the data obtained from the multinational MABEL study (monoclonal antibody Erbitux in European pre-license). The authors' evaluated premedication in relation to response efficacy. A corticosteroid, plus antihistamine, prophylactically administered, resulted in 1% of patients with a grade 3 to 4 reaction, versus 4.7% who received antihistamines alone. The grading and terms employed to describe reactions were based on The Medical Dictionary for Regulatory Activities (MedDRA v8.1); the grade 3-4 reactions were mainly hypersensitivity and dyspnea (Siena et al., 2010). It was concluded that patients susceptible to infusion reactions should receive a corticosteroid, plus antihistamine premedication, while reducing the infusion rate to maintain therapeutic efficacy (Siena et al., 2010). The
unreliability of using an initial test dose to prescreen patients at-risk for an infusion reaction with cetuximab was discussed (Siena et al., 2010).

Schwartzberg, Stepanski, Fortner and Houts (2008) conducted a retrospective chart review (N= 76) of the infusion of three different monoclonal antibodies, focusing on the infusion management and reactions. The premedication of antihistamine, acetaminophen and corticosteroids in combination was examined. Interventions to manage infusion reactions included oxygen, corticosteroids, intravenous fluid resuscitation, antihistamines, epinephrine, H2 blockers and narcotics. The data indicated one-third of patients experienced a rituximab infusion reaction (Schwartzberg, Stepanski, Fortner & Houts, 2008). The consequences of the infusion reactions included dose delays, unplanned hospitalizations and permanent discontinuation of treatment.

Brugger (2010) published a case report that described exchanging cetuximab (chimeric monoclonal antibody) for the fully humanized monoclonal antibody panitumumab in a patient that had a severe infusion reaction to cetuximab. The initial infusion of cetuximab consistently showed mild to moderate reactions at a rate of 16%-19%, whereas, panitumumab had a 1%-3% incidence of reaction (Brugger, 2010). This limited case report demonstrated that even without premedication, panitumumab was well-tolerated, with a low rate of infusion reaction, adding to the growing list of treatment options for post-severe infusion reactions (Brugger, 2010).

Heun and Holen (2007) presented in a case report, replacing cetuximab with panitumumab, when a severe infusion reaction was experienced. Panitumumab and cetuximab target the same epidermal growth factor receptor that is linked to increased
metastasis and a poor prognosis (Heun & Holen, 2007). The severe infusion hypersensitivity reactions observed with cetuximab were not observed with panitumumab. It was speculated that the hypersensitivity reactions were due to the murine component (mouse protein) in cetuximab.

Lenz (2007) conducted a literature review outlining the therapeutic management of and preparedness for infusion reactions, including monoclonal antibodies. Hypersensitivity reactions are unpredictable, necessitating immediate intervention and the availability of standing orders and a crash cart (Lenz, 2007). Lenz (2007) placed importance on the accuracy of grading the severity of the infusion reaction to determine if a re-challenge of the infusional agent is an option.

Brennan, Bouza, Hsu, Sloane and Castello (2009) studied desensitization procedures in 23 patients experiencing hypersensitivity infusion reactions and concluded that rapid desensitization was a promising method to rechallenge monoclonal antibodies after an infusion reaction. The investigators performed an elaborate evaluation to determine appropriate patients, classifications of past infusion reactions and skin hypersensitivity testing to select the participants. A twelve-step desensitization process was used to successfully administer 105 rapid desensitizations (Brennan, Bouza, Hsu, Sloane & Castello, 2009). The desensitization consisted of one-on-one nursing, premedication and the use of three different concentrated solutions of the monoclonal antibody. The rate of each solution was increased 2 to 2 1/2 fold until the target concentration and rate was achieved (Brennan et al., 2009).
Discussion

The evidence supports a conclusion that monoclonal antibodies have an increased risk of infusion reaction, particularly with the initial infusion. The etiology of infusion reactions is complex. Vogel (2010) explained that monoclonal antibodies cause the release of cytokines when a targeted cell is destroyed. This cytokine release mimics a type I hypersensitivity reaction in appearance alone; however, the timing of the release is not similar to a type-1 reaction since the symptoms associated with a cytokine release syndrome subside with each subsequent infusion (Vogel, 2010).

The highest tumor burden is at the initial infusion of the monoclonal antibody. Although Kang and Saif (2007) agreed with the cytokine release syndrome, their focus was on the percent of mouse protein in the monoclonal antibody that caused an immunological response resulting in infusion reactions. IgE-mediated severe infusion reactions in later secondary or subsequent infusion cycles had a short time of onset, suggestive of a type-I hypersensitivity reaction (Kang and Saif, 2007). Patel et al. (2006) agreed that the smaller the percentage of mouse protein per monoclonal antibody the less immunogenicity. Patel et al. (2006) supported the evidence that a monoclonal antibody infusion reaction does not suggest IgE mediation, because the reactions typically happen at the initial infusion and a re-challenge of the medication was successful.

The literature provides evidence to answer two remaining questions, “How can oncology nurse practitioners predict and manage infusion reactions from monoclonal antibodies to diminish the clinical consequences of these reactions?” And, “Is there a
particular population that is more prone to infusion reactions than others?" Chung
(2008) identified factors that predict reactions during initial infusions as, a high
lymphocyte count and presence of IgE-C. O'Neil et al. (2007) suggested there is a
geographical predominance to infusion reactions associated with living in the United
States middle south, stating reactions are due to a prior exposure to mouse protein and
that a geographical risk assessment should be obtained prior to the initial infusion.
Reidy et al. (2007), Tuthill et al. (2009) and Zahrani et al. (2009) concluded that a rapid
infusion of monoclonal antibodies does not contribute to infusion reactions.
Interestingly, Schwartzberg et al. (2009) concluded the opposite, positing a direct
positive relationship between faster infusion time and a higher incidence of infusion
reactions. Reactions resulted in patients spending more time in clinic, increasing their
healthcare costs and adding staff time.

George et al. (2010), Sienna et al. (2009) and Schwartzberg et al. (2007)
supported the use of premedication of at least a corticosteroid in combination with an
antihistamine for prevention of infusion reactions. George et al. (2010) recommended a
test dose to detect hypersensitivity prior to the infusion of a monoclonal antibody.
Premedication prevents adverse infusion reactions, reduces complications from dose
delays, reduces the need for additional staff resources and increases over all cure
rates.

Brugger (2010), Heun and Holen (2007) supported the option of replacing the
monoclonal antibody cetuximab with panitumumab, due to the latter's lower reaction
rate and more successful outcomes. Lenz (2007) recommended immediate intervention,
clear policies and procedures, preparedness for infusion reactions with standing orders.
and a crash cart in close vicinity when dealing with potential infusion reaction victims. Another key to immediate intervention is patient education pertaining to the symptoms that signal an infusion reaction and early communication to the nursing staff of any physical changes experienced during an infusion. Many times, treatment options are limited when a medication must be administered that is specific to the type of cancer. Brennan et al. (2009) explained a desensitization protocol that successfully accomplished completion of infusion post reaction making rechallenge of monoclonal antibodies possible.

**Significance to Nurse Practitioners**

Patient symptom management is the key to reducing life-threatening reactions and for overall treatment success. Dodd and colleagues model of symptom management informs the nursing care related to infusion reactions. It conceptually links infusion reaction, the prediction of reactions and the pre-screening for hypersensitivity to the appropriate management of infusion reactions.

Infusion reactions affect all aspects of the healthcare system (staffing, costs, and resources) making management of this symptom a priority. Nursing goals can be targeted to educate staff on the etiology and risk factors of infusion reactions, and create a process for evaluating and obtaining a baseline assessment and identification of patients at risk (Vogel 2006). It is important to establish a greater understanding of the underlying nature of the events in order to identify patients at risk and to provide symptom management and optimal prophylaxis (Chung, 2008). Moreover, standardized clinic or unit procedures and policies are required for the proper administration of
interventions that help mitigate severity of infusion reactions (Patel, 2006). Clinical pathways, care directives and planned, well-rehearsed responses to infusion reaction events ultimately reduce the negative consequences of infusion reactions, dose delays, hospitalization and permanent discontinuation of treatment (Schwartzberg et al., 2007). The inter-relationships among all of these aforementioned clinical factors can be elaborated by using the symptoms management model.

**Recommendations for Future Research**

The risk of infusion reactions with monoclonal antibodies continues to influence patient outcomes. Kang and Saif (2007) suggested that more research is needed to identify risk factors for severe infusion reactions and to achieve a better understanding of the pharmacokinetics of monoclonal antibodies. O’Neil et al. (2007) argued that further investigation of more specific predictors of hypersensitivity reaction in the United States middle south region is warranted. Additional research is needed prior to routine substitution of panitumumab for cetuximab, along with further studies to understand the etiology of hypersensitivity reaction to validate the benefit of a test dose and IgE testing to predict high risk patients (George et al., 2010). Siena et al. (2007) concluded that a study comparing histamine and corticosteroid premedication versus histamine alone would be helpful in further strengthening the evidence of need of prophylaxis. Schwartzberg et al. (2007) suggested that future studies should determine the direct cost of infusion reactions and related hospitalizations.
References


Figure 1. Symptom Management Model

### Table 1. Summary of Literature Review

#### Factors that Cause Infusion Reactions

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<th>Type of Research</th>
<th>Conclusions</th>
</tr>
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<tbody>
<tr>
<td>Vogel (2010)</td>
<td>Meta-Analysis</td>
<td>Reactions are due to an immune response or cytokine release reaction</td>
</tr>
<tr>
<td>Kang and Saif (2007)</td>
<td>Literature Review</td>
<td>Correlation between mouse protein and cytokine release reaction</td>
</tr>
<tr>
<td>Patel et al. (2006)</td>
<td>Meta-Analysis</td>
<td>Relationship between prior mouse protein exposure and reaction</td>
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**Factors that Predict Infusion Reactions**

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<tr>
<th>Authors</th>
<th>Type of Research</th>
<th>Conclusions</th>
</tr>
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<tbody>
<tr>
<td>Chung (2008)</td>
<td>Literature Review</td>
<td>Infusion reactions typically happen with first infusions, elevated levels of</td>
</tr>
<tr>
<td>O’Neil et al. (2007)</td>
<td>Chart Review (N= 88)</td>
<td>Increased risk of infusion reaction with prior exposure to mouse protein</td>
</tr>
<tr>
<td>Reidy et al. (2007)</td>
<td>Retrospective Chart Review (N= 1077)</td>
<td>Faster rate of infusion does not contribute to increased rate of reaction</td>
</tr>
<tr>
<td>Tuthill et al. (2009)</td>
<td>Research Study (N= 54)</td>
<td>Rapid infusion of 60 minutes equals safe administration</td>
</tr>
<tr>
<td>Zahrani et al. (2009)</td>
<td>Case Report (N= 21)</td>
<td>Rate of infusion does not contribute to increased rate of reactions</td>
</tr>
<tr>
<td>Schwartzberg et al. (2009)</td>
<td>Research Study (N= 161)</td>
<td>35% of infusions reacted to shorter infusion times</td>
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</table>
### Management of Infusion Reactions

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<tr>
<th>Authors</th>
<th>Type of Research</th>
<th>Conclusions</th>
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<tbody>
<tr>
<td>George et al. (2010)</td>
<td>Research Study (N=54)</td>
<td>Recommend test dose, premedication with corticosteroids, H1 antagonist and consider substitution of panitumumab</td>
</tr>
<tr>
<td>Siena et al. (2009)</td>
<td>Post Hoc Analysis</td>
<td>Test dose is not reliable, premedicate with corticosteroid and antihistamine</td>
</tr>
<tr>
<td>Schwartzberg et al. (2008)</td>
<td>Retrospective Chart Review (N= 76)</td>
<td>Premedicate with antihistamine, acetaminophen and corticosteroids. Manage reaction with O2, corticosteroids, IV fluid, antihistamines, epinephrine, H2 blockers and narcotics</td>
</tr>
<tr>
<td>Brugger (2010)</td>
<td>Case Report</td>
<td>Without premedication, panitumumab was well tolerated in exchange for cetuximab</td>
</tr>
<tr>
<td>Heun and Holen (2007)</td>
<td>Case Report</td>
<td>The severe reactions seen with cetuximab were not seen with panitumumab</td>
</tr>
<tr>
<td>Lenz (2007)</td>
<td>Literature Review</td>
<td>Reactions are unpredictable, requiring immediate intervention and accurate grading of the reaction</td>
</tr>
<tr>
<td>Brennan et al. (2009)</td>
<td>Research Study (N= 105)</td>
<td>Desensitization is a promising method for rechallenge</td>
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